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CANCER OF THE BREAST

A REPORT OF FIVE-YEAR SURVIVAL AT THE UNIVERSITY OF MICHIGAN HOSPITAL

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IN THE twelve-year period 1936 through 1947, a total of 1,227 patients with carcinoma of the breast were seen at the University Hospital. During this period, and at the present time, radical mastectomy as advocated by Halsted has been the treatment of choice for operable cancer of the breast. In recent years certain groups have recommended that the surgical treatment of breast cancer be expanded, while other groups have taken the opposite viewpoint and advised contraction. We have had no experience with the "super" radical operations as described by Wangensteen[1] and Urban,[2] nor have we had experience with elective simple mastectomy and postoperative irradiation as advised by McWhirter.[3]

In 1902 Winter[4] published a memorable paper concerning the proper methods in reporting the results of cancer therapy. He stressed the point that the total number of patients seen must be reported, and subsequent to treatment the patients should be followed for an indefinite period of time. It would seem fundamental that in any report all figures should be included, and if the statistics are broken into specific groups, this should be clearly indicated. This basic information is unfortunately not included in many reports which attempt to assess the long-term survival rates following treatment of breast cancer.

In 1933 the Cancer Committee of the University of Michigan established a program for the collection of factual data on each malignant neoplasm encountered at the University Hospital.[5] An integral part of this program has been carried out by the Social Service Department. With their assistance we have been able to obtain at least a five-year follow-up on all the patients included in this report. Each patient has had an annual checkup examination in the outpatient clinic, or a factual report has been obtained by letter from the

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patient or her personal physician. In a small number of cases it was necessary to obtain information from the County Recorder of Vital Statistics or from the patient's relatives.

RESULTS

A total of 1,227 patients were seen during the period 1936 through 1947 (inclusive). Of these patients, 431 were seen at various intervals following primary treatment elsewhere. The majority of this group was referred to the University Hospital because of recurrence, either locally or as distant metastases. A few patients had their radical mastectomy at an outside hospital and were then referred here for postoperative irradiation. An additional forty-five patients came only for consultation, and for various reasons, nine patients refused treatment of any type.

The number of patients considered to be in the group of primary untreated cases was 742. Of these, 709 had their entire treatment at the University Hospital. Thirty-three patients had the mastectomy at the University Hospital; however, postoperative irradiation was given by a radiologist in their home community. In this primary untreated group, 298 patients were alive five or more years after their operations, a five-year survival rate of 40.2 per cent. Fifty-two of these patients were alive with clinical or roentgenographic evidence of recurrence of the tumor. Exclusion of these fifty-two patients gives a five-year "clinical cure" rate of 33.2 per cent (Table I). All patients who died within the five-year period following treatment were considered to have died from recurrent cancer. The five-year survival rate of 40.2 per cent (or clinical cure rate of 33.2 per cent) represents the total survival achievement over all patients, in all stages of extent of the disease, who came to this institution without previous treatment.

TABLE I

Total no. patients seen	1,227
No. with previous treatment	431
No. left for treatment elsewhere	45
No. refused treatment	9
No. untreated on admission	742
No. alive 5 yr. without evidence of Ca	246
No. alive 5 yr. with Ca	52
5-yr. survival: $\frac{298}{742} = 40.2\%$	
5-yr. clinical cure: $\frac{246}{742} = 33.2\%$	

Of the primary untreated cases, 440 patients were considered candidates for radical mastectomy, an operability rate of 59.3 per cent. A few patients had preoperative irradiation followed by radical mastectomy, but these patients were all questionable surgical candidates and have not been considered operable.

The entire group of 440 patients who were considered clinically operable were treated by radical mastectomy. In this group, 145 patients did not have postoperative irradiation while 295 patients did have x-ray therapy following operation. The five-year survival rate for this entire group was 58.4 per cent, and the five-year clinical cure rate was 50.7 per cent (Table II). If the thirty-three patients who had their postoperative irradiation elsewhere are excluded, the five-year survival rate is 60.4 per cent for patients receiving all of their therapy at the University Hospital, and the five-year clinical cure rate is 52.8 per cent (Table III); the differences are not significant.

TABLE II

No. radical mastectomies, with and without P.O. x-ray treatment	440
(Operability: $\frac{440}{742} = 59.3\%$)	
No. alive 5 yr. without evidence of Ca	223
No. alive 5 yr. with Ca	34
5-yr. survival: $\frac{257}{440} = 58.4\%$	
5-yr. clinical cure: $\frac{223}{440} = 50.7\%$	

TABLE III

Patients treated entirely at University Hospital	
No. radical mastectomies (excluding 33 patients given P.O. x-ray treatment elsewhere)	407
No. alive 5 yr. without evidence of Ca	215
No. alive 5 yr. with Ca	31
5-yr. survival: $\frac{246}{407} = 60.4\%$	
5-yr. clinical cure: $\frac{215}{407} = 52.8\%$	

In 45 per cent of the patients operated upon, routine examination of the axillary contents by our pathologist disclosed no microscopic carcinoma. The five-year survival rate of these patients without histologic evidence of axillary spread is 82.7 per cent, and the five-year clinical cure rate is 75.6 per cent (Table IV). Table V considers only the patients receiving all of their treatment at the University Hospital and shows little change from the previous figures.

TABLE IV

Radical mastectomies with and without P.O. x-ray treatment	
Negative Axilla	
No. patients with negative axilla	197
No. alive 5 yr. without evidence of Ca	149
No. alive 5 yr. with Ca	14
5-yr. survival: $\frac{163}{197} = 82.7\%$	
5-yr. clinical cure: $\frac{149}{197} = 75.6\%$	

TABLE V

Patients treated entirely at University Hospital	
Radical mastectomies with and without P.O. x-ray treatment (excluding 7 patients given P.O. x-ray treatment elsewhere)	
No. patients with negative axilla	190
No. alive 5 yr. without evidence of Ca	145
No. alive 5 yr. with Ca	12
5-yr. survival: $\frac{157}{190} = 82.6\%$	
5-yr. clinical cure: $\frac{145}{190} = 76.3\%$	

It seems reasonable to question the use of irradiation postoperatively in patients without microscopic evidence of carcinoma in axillary nodes. In earlier patients in this series, irradiation, whether or not axillary metastases were present, was used almost routinely in the postoperative period. More recently, irradiation has been discontinued in these patients. The five-year survival rate of patients who did not receive postoperative irradiation, in the presence of a negative axilla, was 80.2 per cent, while for those receiving irradiation it was 84.9 per cent. The clinical cure rate was 72.5 per cent and 78.3 per cent in the two comparable groups (Table VI). The survival rate, using the chi square test, was not significantly different in the two groups. Patients treated only at the University Hospital are shown in Table VII, and the results vary little from the previous figures.

TABLE VI

Radical mastectomies: Surgery versus surgery plus P.O. x-ray treatment	
Negative Axilla	
No. surgery only	91
No. alive 5 yr. without evidence of Ca	66
No. alive 5 yr. with Ca	7
5-yr. survival: $\frac{73}{91} = 80.2\%$	
5-yr. clinical cure: $\frac{66}{91} = 72.5\%$	
No. surgery plus x-ray treatment (including P.O. x-ray treatment elsewhere)	106
No. alive 5 yr. without evidence of Ca	83
No. alive 5 yr. with Ca	7
5-yr. survival: $\frac{90}{106} = 84.9\%$	
5-yr. clinical cure: $\frac{83}{106} = 78.3\%$	

Two hundred forty-three or 55 per cent of the patients had positive axillary nodes. In Table VIII it is to be noted that a five-year survival rate of 38.7 per cent and a five-year clinical cure rate of 30.5 per cent was obtained. The results are not significantly different when those patients receiving postoperative irradiation elsewhere are excluded (Table IX).

If we compare the patients with positive axillary nodes having radical surgery alone with those having radical surgery plus postoperative irradiation, we note that the survival and clinical cure rates are approximately the same. The surgically treated group showed a five-year survival rate of 38.9 per cent and a five-year clinical cure rate of 33.3 per cent. These results compare favorably with figures of 38.6 per cent and 29.6 per cent, respectively, for those receiving surgery plus x-ray therapy (Table X). If the twenty-six patients who received postoperative x-ray therapy elsewhere are excluded from the group, there is a 41.7 per cent five-year survival rate and a 31.9 per cent five-year clinical cure rate (Table XI).

TABLE VII

Patients treated entirely at University Hospital

Negative Axilla

No. surgery plus x-ray treatment (excluding 7 patients given P.O. x-ray treatment elsewhere)	99
No. alive 5 yr. without evidence of Ca	79
No. alive 5 yr. with Ca	5

5-yr. survival: $\frac{84}{99} = 84.8\%$

5-yr. clinical cure: $\frac{79}{99} = 79.8\%$

TABLE VIII

Radical mastectomies with and without P.O. x-ray treatment

Positive Axilla

No. patients with positive axilla	243
No. alive 5 yr. without evidence of Ca	74
No. alive 5 yr. with Ca	20

5-yr. survival: $\frac{94}{243} = 38.7\%$

5-yr. clinical cure: $\frac{74}{243} = 30.5\%$

TABLE IX

Patients treated entirely at University Hospital

Radical mastectomies with and without P.O. x-ray treatment (excluding 26 patients given P.O. x-ray treatment elsewhere)

No. patients with positive axilla	217
No. alive 5 yr. without evidence of Ca	70
No. alive 5 yr. with Ca	19

5-yr. survival: $\frac{89}{217} = 41.0\%$

5-yr. clinical cure: $\frac{70}{217} = 32.3\%$

TABLE X

Radical mastectomies: Surgery versus surgery plus P.O. x-ray treatment	
Positive Axilla	
No. surgery only	54
No. alive 5 yr. without evidence of Ca	18
No. alive 5 yr. with Ca	3
5-yr. survival: $\frac{21}{54} = 38.9\%$	
5-yr. clinical cure: $\frac{18}{54} = 33.3\%$	
No. surgery plus x-ray treatment (including P.O. x-ray treatment elsewhere)	189
No. alive 5 yr. without evidence of Ca	56
No. alive 5 yr. with Ca	17
5-yr. survival: $\frac{73}{189} = 38.6\%$	
5-yr. clinical cure: $\frac{56}{189} = 29.6\%$	

TABLE XI

Patients treated entirely at University Hospital	
Positive Axilla	
No. surgery plus x-ray treatment (excluding 26 patients given P.O. x-ray treatment elsewhere)	163
No. alive 5 yr. without evidence of Ca	52
No. alive 5 yr. with Ca	16
5-yr. survival: $\frac{68}{163} = 41.7\%$	
5-yr. clinical cure: $\frac{52}{163} = 31.9\%$	

DISCUSSION

Indications and contraindications to radical mastectomy are not absolute since they are always subject to individual interpretation. Our contraindications agree rather closely with those listed by Haagensen.[6] Pregnancy and lactation are not considered an objection to surgical treatment. In the early years of this study, a small number of patients had a simple or modified mastectomy because of advanced age or because of medical contraindications to operation. With better pre- and postoperative care, some of these patients would now be reasonable surgical risks for the radical operation. There were no postoperative deaths among the 440 patients who had radical mastectomy.

The pronounced difference in survival rate for patients with and without positive axillary nodes emphasizes the importance of early diagnosis. Many surgical textbooks still stress the advanced signs and symptoms of breast cancer. It must be emphasized that any discrete lump in the breast should be surgically removed in the operating room and subjected to frozen section and study by the pathologist. If a diagnosis of cancer is made, one may then proceed immediately with mastectomy and removal of the pectoral muscles and

the axillary contents. By this procedure, unnecessary delay in definitive treatment is avoided, and repeated discomfort and expense to the patient are minimized.

During more recent years we have questioned the use of routine postoperative irradiation. The statistics presented here show no significant benefit in the survival rates of those treated with postoperative irradiation as compared to those who received surgical treatment alone. Postoperative irradiation is now reserved for those patients with overwhelming axillary involvement, with involvement of the axillary nodes at the extreme axillary apex, or in those instances in which the surgeon is certain that axillary extension of carcinoma was incompletely removed. The postoperative irradiation which has been used is carried out with 200 kv. radiation of half-value layer 1.0 mm. copper at a distance of 50 cm., treating four fields directed toward the axillary pyramid and achieving a dose in the middle of this pyramid of about 5,000 r in three and one-half weeks. It must be emphasized that our present attitude regarding the use of postoperative radiation treatment is based on the use of an adequate radical surgical operation and does not necessarily apply when operative procedures of lesser extent are employed.

Careful preoperative evaluation and preparation of these patients is essential. Routine roentgenograms of the chest, spine, pelvis, and upper long bones are always made to rule out distant silent metastases. The use of atraumatic surgical technique and meticulous dissection of the axillary contents is routine in this clinic. Skin grafting has not been routinely practiced. Adequate removal of the skin and primary closure have been possible in most instances. At the present time we place one or two suction catheters into the depths of the axillae and maintain constant suction with an electric suction pump for several days postoperatively. The accumulation of fluid under the widely dissected skin flaps is minimized by the use of these double-lumen suction catheters. A dressing is applied to the wound so as to maintain constant, even pressure which does not interfere with respiration. Early graduated motion of the shoulder is begun shortly after operation, and patients are ideally discharged from the hospital on the tenth or twelfth postoperative day. Postoperative edema of the arm has not been a frequent problem.

SUMMARY AND CONCLUSIONS

1. The experience at the University Hospital with 1,227 cases of breast cancer seen between 1936 and 1947 (inclusive) has been presented.

2. The over-all five-year survival rate of 742 primary untreated patients was 40.2 per cent.

3. Four hundred forty patients were candidates for radical mastectomy, an operability rate of 59 per cent. The five-year survival rate of this group of patients was 58 per cent.

4. Forty-five per cent of the patients treated by radical mastectomy had negative axillary nodes upon histologic examination. The survival rate at the end of five years for this group was 82.7 per cent.

5. Patients with positive axillary nodes had a five-year survival rate of 38.7 per cent.

6. Our statistics do not support the routine use of postoperative irradiation when a complete radical mastectomy is performed.

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BILATERAL ADRENALECTOMY IN THE TREATMENT OF ADVANCED CARCINOMA OF THE BREAST

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THE adrenal glands within the past few years have claimed a tremendous amount of attention, and current literature dealing with their physiologic functions and the application of their therapeutic derivatives is rapidly reaching astronomic proportions. During this time, the relationship of cancer of the prostate and breast to adrenal function has been recognized, but published data to date have been relatively meager. The recording of further observations relating to this subject, even though limited, seems justified.

The value of removing gonads and adrenal glands in the treatment of cancer is based on the fact that when the tissue in which malignancy develops is functionally dependent upon hormones, this property may be transmitted to neoplasms arising in such tissue. Such malignancies may be stimulated or inhibited by the administration or withdrawal of appropriate endocrine substances. This is not a new concept, as some may believe, because Beatson[1] in 1896 observed regression of mammary cancer in two cases following oophorectomy. The surgical removal of ovaries in the treatment of breast cancer was gradually supplanted by irradiation when it was learned that ovarian function could be destroyed in this manner, even though it is a much slower and less certain method of eliminating ovarian function.

Since the work of Huggins and associates in 1939,[11] it has been known that the inhibition of androgenic production, or action by the administration of estrogen or by orchiectomy, has had a favorable result in many cases in the treatment of carcinoma of the prostate. In some instances, favorable results by such methods have not been obtained or remissions have been of short duration, and it has been postulated that organs other than the testes may produce androgens. Experimental work on laboratory animals suggested this possibility, and clinical observations have corroborated this viewpoint. For instance, androgenic tumors occurring in the adrenal cortex of women and boys before puberty have been observed to produce masculinization, with regression of these characteristics when such tumors were removed. A study of urinary excretion of 17-ketosteroids by Scott and Vermeulen[2] showed that following castration, a reduction occurred frequently followed by a level at least twice that previous to castration, and this rise suggested an extra gonadal source, in all probability arising in the adrenal glands.

A number of bilateral adrenalectomies were carried out by Huggins and Scott[3] from 1942 to 1944 in patients who had previously responded to castration or estrogen therapy, but who had relapsed. However, adequate replacement therapy for adrenal deficiency was not available at this time, and the

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procedure was abandoned because of the development of Addisonian crises and other complications that could not be coped with adequately. In 1951, Thorn and associates,[4] who apparently were the first to succeed in maintaining life for any appreciable length of time following bilateral adrenalectomy, by the use of desoxycorticosterone acetate and cortisone acetate, pointed out the effectiveness of cortisone given orally. Following these observations, Huggins and Bergenstal[5] were encouraged to re-evaluate the procedure of bilateral adrenalectomy in cases of relapse following castration and estrogen therapy for advanced prostatic carcinoma. At the meeting of the American Surgical Association in April, 1952, Huggins presented a paper on adrenalectomy for mammary cancer with observations on forty-two cases of bilateral adrenalectomy, eight of which were for advanced mammary cancer. Later in the same year, having received a personal communication from Dr. Huggins in which he stated he was increasingly enthusiastic about bilateral adrenalectomy for advanced mammary cancer, and in which he also included his method of pre- and postoperative handling of such patients, we were encouraged to give this method of procedure a trial. Since Dec. 12, 1952, we have performed nine bilateral adrenalectomies for advanced metastatic malignancy, eight of which proved to be secondary to breast carcinoma. Our experience with these cases will be commented upon later in this paper.

In April, 1953, Huggins and Dao[6] reported an experience with fifty-five patients having advanced mammary cancer treated by adrenalectomy, two of whom were men. Their conclusions in brief were as follows:

1. The ovary is strongly implicated in the maintenance of mammary carcinoma in the human female. The relative function of each of the ovarian hormones is not well understood.

2. The widespread use of estrogen has not appreciably increased breast cancer.

3. The involution of mammary cancer after oophorectomy is clearly due to removal of ovarian hormones produced by the ovary, and the most plausible explanation of beneficial effects of adrenalectomy is elimination of hormones of a similar nature.

4. The excretion of estrogen in urine of women who have undergone oophorectomy is abolished by adrenalectomy.

5. The microscopic appearance of the neoplasm is frequently of value as a first approximation in differentiating between dependent and nonresponsive cancers.

6. Most mammary cancers, predominantly papillary neoplasms or adenocarcinomas, regressed after these surgical procedures. Duct carcinomas rarely and undifferentiated mammary cancers never responded favorably.

7. High titer values of estrogenic substances in the urine in the absence of gonadal function indicate adrenal cortical activity of significance in mammary cancer.

From the evidence accumulated in this series of cases, Huggins and Dao came to the conclusion that oophorectomy and adrenalectomy have more to

offer in the treatment of advanced metastatic malignancy of mammary origin than any other method available to date.

In a recent article by Butler and associates,[7] metabolic studies were reported in two advanced carcinomas of the prostate treated by removal of the gonads and bilateral adrenalectomy. Their conclusions were as follows:

Bilateral adrenalectomy can now, by the use of cortisone, be a safe and valuable procedure and may prove to be of great value in the therapy of carcinoma of the prostate, hypertension, and diabetes mellitus, but until the physiology of the adrenalectomized patient is better understood, it must be restricted to cases in the hopeless category. By the use of 25 to 50 mg. of cortisone given orally each day, acid-base balance remains in equilibrium when renal function is normal and the diet is adequate and contains 6 Gm. of sodium chloride. It was found that desoxycorticosterone acetate is not usually required to maintain the patient, and may be contraindicated, as shown by studies of total sodium and potassium excretion. Glucose tolerance is increased after bilateral adrenalectomy when cortisone dosage is 25 mg. a day. Alkaline and acid phosphatases indicated improvement in the cases studied, as did their ability to maintain total serum protein and hemoglobin values. The administration of testosterone increased the adrenocortical requirement in one individual and precipitated an Addisonian crisis on two occasions.

Krieger and colleagues[8] have recently reported on the data obtained from a study of five patients with metastatic carcinoma treated by bilateral adrenalectomy. The primary site of the carcinoma was mammary in three, prostatic in one, and the fifth patient had widespread melanosarcoma. They found it unnecessary to give desoxycorticosterone acetate in the preoperative preparation of the patients or to add extra sodium chloride to their diets. The operation was well tolerated by all the patients, and after the first few postoperative days, other than the administration of cortisone, they were managed in the same manner as any other postoperative patient. Three patients demonstrated subjective temporary improvement, and objectively this improvement was best demonstrated by correction of negative calcium balance and hypercalcemia. No demonstrable influence on the clinical course of the patient with melanosarcoma was noted.

In the nine cases of bilateral adrenalectomy being reported (all women), there were no surgical deaths, but three patients have subsequently died of their disease: one, sixty-seven days, one, ninety-four days, and one, ten months postoperatively. One individual has shown such dramatic clinical improvement that a brief résumé of her case is of interest.

CASE 1.—A white Caucasian woman, aged 62 years, had a right radical mastectomy on June 1, 1951. Wide removal of skin necessitated a skin graft. Axillary lymph nodes were reported negative for metastases. The pathologist reported the lesion to be an undifferentiated carcinoma (Fig. 1). The patient made an uneventful recovery, but seventeen months later, examination revealed multiple small nodules in the skin graft (Fig. 2). Six of these nodules were removed, and all showed carcinoma. For the previous two months, the patient had complained of pain in the back, and x-ray studies showed a destructive process involv-

ing the fifth and sixth ribs on the right and the right ilium (Fig. 3, *A* and *B*). The patient was subjected to x-ray therapy to these involved areas, and she was started on hormone therapy, but the pain became progressively more severe.

On Dec. 2, 1952, eighteen months after mastectomy, the patient was admitted to the hospital on a stretcher. She was in excruciating pain, except when under narcotics, and she was bedridden. A bilateral adrenalectomy was performed on Dec. 12, 1952, with almost immediate relief of pain, and she was able to leave the hospital ten days later. Ten months following adrenalectomy, she had gained 25 pounds in weight, had been free of pain since leaving the hospital, and she was able to get about without the aid of crutches or a cane.

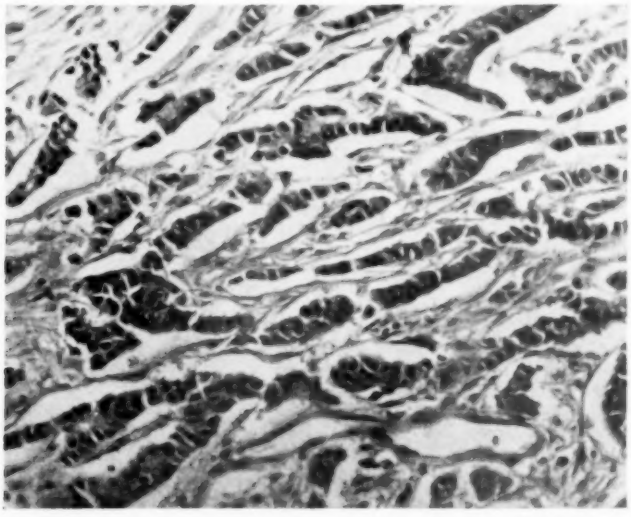


Fig. 1.—Microscopic picture of primary lesion, Case 1.

Fig. 2.—Photograph showing metastatic carcinoma in grafted skin after radical mastectomy.

In spite of this marked clinical improvement, x-ray investigation on Jan. 7, 1954, showed marked progression of the osseous involvement in the pelvis (Fig. 3, *C*). To date, fourteen months after operation, the patient continues much the same although she has lost some weight, and it may mean that the remission in the disease is near an end. Another observation worth mentioning is that for years the patient had been hypertensive, blood pressures of 200/110 being frequently recorded, and since adrenalectomy, her blood pressure has averaged around 130/90.

CASE 2.—Another case of interest was of a Caucasian woman, 38 years of age at the time of radical mastectomy on Dec. 3, 1940. The pathologic report of the primary lesion was: scirrhous carcinoma, Grade II to III, probably fitting into the category that Huggins calls duct cell carcinoma (Fig. 4). Axillary lymph nodes were reported to be negative. On Aug. 31, 1951, approximately ten years and nine months after the mastectomy, exploration of the abdomen was carried out for a palpable mass causing partial intestinal obstruction. Extensive carcinomatosis was found involving the omentum, intestines, abdominal wall, and pelvic organs. A biopsy showed Grade II adenocarcinoma. The patient was given x-ray therapy to the abdomen and hormones, consisting of Oreton, 100 mg. doses, until marked physiologic effects were noted. Further x-ray therapy in May, 1952, was given at Memorial Hospital in New York. Subsequent to this, abdominal paracentesis was carried out repeatedly, 300 to 1,600 c.c. of milky (chyle) fluid being removed.

On Dec. 16, 1952, a bilateral adrenalectomy was performed because more conservative measures had failed to halt the progress of the disease. On Jan. 5, 1953, 700 c.c. of fluid was aspirated from the abdomen, and 1,500 c.c. on June 6, 1953. The fluid was noted to be decidedly clearer than previously. On Sept. 17, 1953, the patient was hospitalized and given several blood transfusions because of a severe gastric hemorrhage, later shown by x-ray studies to be due to a penetrating ulcer in the prepyloric area on the greater curvature of the stomach. The patient died Oct. 10, 1953, ten months after adrenalectomy, from peritonitis resulting from rupture of the ulcer. Autopsy showed no evidence of carcinoma in the abdominal cavity, but there were metastases to the lung, pleura, and mediastinum.

It was felt, by us at least, that as far as the malignancy was concerned, adrenalectomy had proved of value. The patient did not feel well much of the time following this procedure, but she was able to get about, and attended to her usual active social functions. The occurrence of ascites had largely subsided, and at autopsy, no evidence of the abdominal carcinomatosis remained. No doubt the progress of the gastric ulcer had been stimulated by the administration of cortisone, and I suppose it might have been an etiological factor in its production.

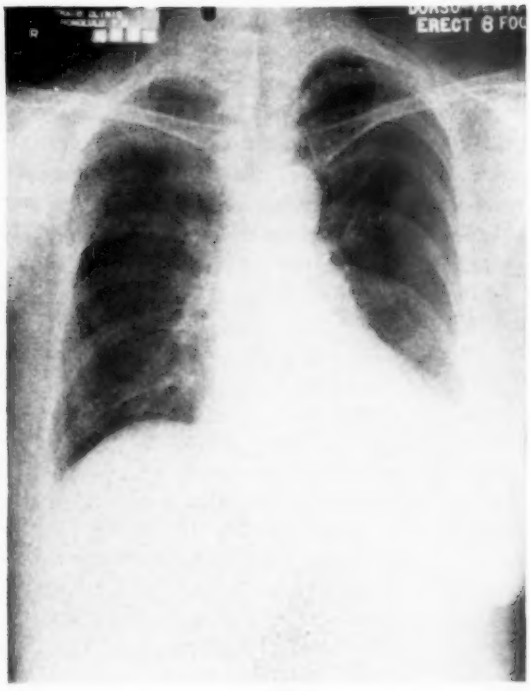
CASE 3.—A third case is of interest even though the period of observation has been only six months following bilateral adrenalectomy.

A Caucasian woman, aged 45 years, had a radical mastectomy for carcinoma of the right breast on Nov. 1, 1949. Two years later, pain began in the right hip and x-ray film revealed a destructive process in this area. She was sterilized by x-ray treatment, started on stilbestrol, and later given other hormones. The progress of the disease continued unabated. X-ray studies on July 8, 1953 (Fig. 5, *A*), showed extensive metastases to ribs, spine, pelvis, and skull. A bilateral adrenalectomy was performed on Aug. 3, 1953.

On Feb. 1, 1954, six months after adrenalectomy, the patient stated in a letter, "I feel very well. I get around as spry as a cricket. I eat well and relish food, and I have gained several pounds in weight." In spite of this favorable report from the patient, x-ray study showed the osseous involvement to be progressive (Fig. 5, *B*).

CASE 4.—The most recent patient had a radical mastectomy for carcinoma on Dec. 9, 1950, at the age of 44 years. Abdominal pain began in the early part of 1953, and continued with increasing severity, the cause of which could not be determined after thorough x-ray investigation, although bone metastases were suspected. Supraclavicular lymph nodes on the left involved with metastatic carcinoma were removed on Nov. 5, 1953. Hormonal therapy produced no improvement.

On Jan. 24, 1954, the patient was admitted to the hospital because of vomiting large amounts of blood associated with abdominal distention and pain. Several blood transfusions were given, and the abdomen was explored. There was much clear straw-colored fluid in the abdominal cavity. There were metastases to the right lobe of the liver and retroperitoneal area. Inspection of the stomach and duodenum, both inside and out, was carried out, and nothing to account for the bleeding was found. Both ovaries were removed, one of which showed metastatic carcinoma.



A.

B.

Fig. 3.—*A*, X-ray film showing involvement of sixth and seventh ribs, right. *B*, X-ray film showing metastases to right ilium, Nov. 10, 1952.

A bilateral adrenalectomy was performed on Feb. 5, 1954. The patient left the hospital on March 3, 1954, feeling much better, eating well, largely relieved of pain. This patient has been observed for only a short period following adrenalectomy, but it is amazing how much clinical improvement has occurred during this time.

C.

D.

Fig. 3.—*C*, X-ray film showing extension of involvement of osseous metastases in pelvis (Jan. 7, 1954) after bilateral adrenalectomy.
D, X-ray film showing skull involvement with metastases, Jan. 7, 1954.

In two other cases, of patients who have died at approximately two and three months postoperatively, both gave evidence of clinical improvement subjectively for several weeks. Their pain was less, and appetite improved. In one of these cases, the finding of carcinoma in the axillary nodes led us to believe that in all probability the primary lesion arose in the associated breast, although no lesion of the breast was demonstrated after a radical mastectomy had been performed. The other three patients of this series have been operated upon too recently to permit of any conclusions being drawn as to the benefits of the adrenalectomy.

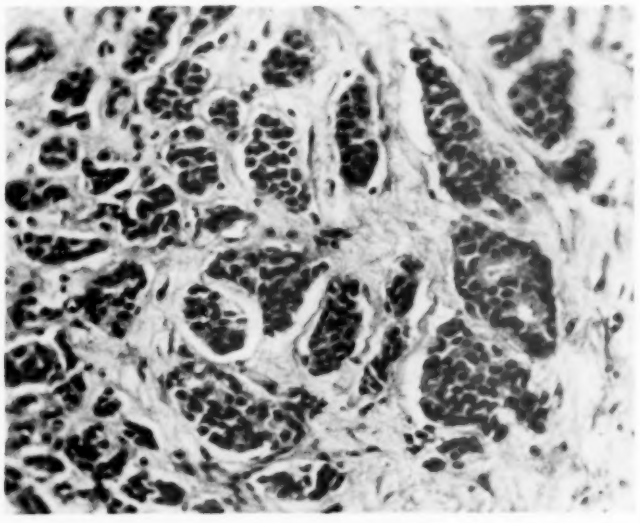


Fig. 4.—Microscopic picture of primary lesion, Case 2.

DISCUSSION

It is obvious that sufficient data have not yet been accumulated to demonstrate just how valuable an adjunct bilateral adrenalectomy is in the treatment of advanced carcinoma of the breast. It can be said without question that it does in certain instances relieve patients of pain, gives most a sense of well-being for a time, and, in addition, no doubt prolongs life in others. No evidence has been accumulated showing that the procedure is a curative one. The ability to select individuals who will benefit from this procedure by the microscopic picture of the primary lesion has not in our limited experience been of significant value. Sections of the primary lesion in each of the patients subjected to adrenalectomy were examined by several pathologists, and there was no unanimity of opinion as to which patients might respond favorably to the procedure, using the histologic criteria suggested by Dr. Huggins. It was their opinion that the Huggins classification is oversimplified and difficult to interpret. Over 90 per cent of all mammary cancer arises from duct epithelium, and 70 per cent of these are of no special type and tend to be very similar histologically. According to the Huggins classification, few breast malignancies in this large group would respond to adrenalectomy, and the papillary and

well-differentiated adenocarcinomas which are thought by Huggins to respond favorably actually constitute a very small percentage of all breast carcinomas. Moreover, many pathologists believe that grading carcinomas as to degree of

A.

B.

Fig. 5.—*A*, X-ray film of pelvis, Case 3, July 8, 1953.
B, X-ray film of pelvis, Case 3, Dec. 11, 1953, showing extension of osseous involvement following adrenalectomy.

differentiation may be unreliable because this frequently differs in various parts of the same tumor; a few random sections may completely fail to give a true picture of the microscopic structure of the tumor.

Pearson and associates,[9] at the Memorial Center in New York, reporting on a series of twenty cases of bilateral adrenalectomy for advanced breast carcinoma, stated, "There are two types of mammary cancer in women: one type is dependent upon estrogen for maintenance of its growth rate; the other type is non-estrogen dependent. These two types of mammary cancer cannot be distinguished by their histologic appearance or from the clinical features of the disease." They reported that calcium excretion studies are a practical guide for determining promptly the response to therapy in patients who have osteolytic metastases. They stated that the growth of 1 Gm. of tumor tissue destroys 1 Gm. of bone, resulting in 100 mg. of calcium being excreted, nearly all of which is excreted in the urine. It is pointed out that precise measurement of calcium balance in patients is a complicated procedure and that the use of the Sulkowitch test has been sufficiently accurate for clinical purposes. Utilizing calcium excretion data obtained by this method, a study was made of six patients in the premenopausal stage with osseous breast metastases, during the menstrual cycle after surgical oophorectomy, and during administration of ovarian hormones. All six patients had hypercalciuria at the beginning of these studies.

In three individuals, calcium excretion in the urine was markedly increased during the menstrual cycle, it decreased to normal levels within the first week after oophorectomy, indicating prompt cessation of osteolysis, and subjective and objective improvement occurred. Administration of estrogen brought about prompt return of bone pain and hypercalciuria, which disappeared with the elimination of estrogen. The other three women responded in an entirely different manner. No fluctuation in urinary excretion of calcium occurred during the menstrual cycle, surgical castration failed to influence the level of calcium excretion, there was no clinical improvement, and skeletal radiographs showed progression of bone metastases.

While we have not made calcium excretion studies in these patients undergoing adrenalectomy, it has been our experience that patients may still show marked clinical improvement even though x-ray studies show bone metastases to be progressive. It would seem that a decision to deny an individual the possible benefits of adrenalectomy should not depend upon the microscopic picture of the primary lesion unless something more definite is found in the future than is evident at the moment, nor should calcium excretion studies be the deciding factor unless and until wider experience has established the soundness of such observations.

Further observation as to the desirability of removing the ovaries in individuals who have undergone artificial menopause induced by irradiation and in individuals who have passed into this stage normally is needed. There is some indication that hormonal activity may persist as long as the ovaries remain, which may stimulate the growth of breast malignancy. Further data are also

needed on the association of the hypophysis with the production of hormones that have a similar action, and on the benefits that may result from the extirpation of this gland.

Maintaining individuals who have been adrenalectomized in a state of normal physiologic balance by the use of oral cortisone has not been a problem so long as no added stress or strain has occurred with which to deal. Increased amounts of cortisone are necessary when these occur.

The death of the individual from perforation of a gastric ulcer emphasizes the necessity for close observation of individuals who have a history of gastroduodenal lesions. Such a history might be a deciding factor against employing bilateral adrenalectomy.

It has been pointed out by various observers that the clinical trial of corticotrophin (ACTH) and cortisone for the treatment of advanced breast cancer has not met with success. Pearson and colleagues[9] have observed three patients castrated without benefit who have obtained remission on doses of 200 to 300 mg. of cortisone per day. Increasing the doses of cortisone to this amount following failure of adrenalectomy or when evidence of progression of the disease returns after a period of remission might be worth trying.

The advisability, even safety, of administering either estrogens or androgens following bilateral adrenalectomy seems to be a matter of controversy at the present time. To evaluate the effectiveness of androgens under these conditions, Butler and co-authors[7] reported that Addisonian crises resulted following the administration of testosterone intramuscularly, and death followed a repeat injection seven weeks later. On the other hand, Pearson and associates[9] stated that when relapse occurs following adrenalectomy, testosterone therapy is worthy of trial, as they have observed an objective remission from testosterone administered in two patients who had previously responded to oophorectomy and adrenalectomy. They stated that the mechanism by which testosterone induces remission in women with breast cancer is unknown. Whether it works by opposing the effects of estrogen or tumor growth cannot be answered at the present time.

The cause of relapse in patients who have shown remission following bilateral adrenalectomy has been thought to be due, in some instances at least, to the fact that bilateral adrenalectomy does not constitute total adrenalectomy in many patients. Graham,[10] at Memorial Hospital in New York, has demonstrated accessory adrenal cortices in the region of the celiac axis in thirty-three of 100 consecutive autopsies. In two of twelve patients of Pearson's series, cortisone withdrawal was not followed by appreciable evidence of adrenal deficiency. In the other ten, an adrenal crisis developed within three to seven days.

The surgical removal of the adrenals has not been found to be difficult, time consuming, or shocking to the patient. An exposure by way of an incision similar to that used for nephrectomy with, at times, removal of the last rib has been found adequate. The characteristic color and shape of the adrenals lying medial to and above the superior renal pole add to the ease of their identification. When involved by metastases, either in the gland or in the surrounding tissue,

the difficulty of their removal is increased. It is imperative that the entire gland be removed, but no difficulty has been experienced in this respect because the adrenals have always been well delineated. Both adrenals have been removed at one operation, and the usual time required has been around eighty to ninety minutes. No alarming fall in blood pressure has occurred, and postoperative recovery has been uneventful. In one individual, the ovaries were removed at the time of the bilateral adrenalectomy, and in one other, approximately ten days previous to adrenalectomy. In the others, the patient had either undergone menopause or had had artificial menopause induced by irradiation.

In general, we have followed the method of preoperative preparation and postoperative care advocated by Huggins and associates. In one individual, desoxycorticosterone acetate was not used because, at the time, it was not available. The patient's course was uneventful. We have not found that the sodium chloride intake need be different from that of the normal individual and have noted no untoward effects from the patient's pursuing a usual diet.

IMPRESSIONS

One is not justified in drawing conclusions based on so limited an experience as ours has been. The purpose of this presentation has not been to do more than add to the sum total of the experience of others, feeling that, by so doing, enough clinical material will ultimately be accumulated to permit the proper evaluation of adrenalectomy in the treatment of advanced mammary cancer. At the moment, we believe that adrenalectomy has a place in the treatment of such breast cancers when other more conservative measures have failed to halt the progress of the disease. We believe that to date no method exists that will permit the selection of the individual who will or will not benefit from such a procedure, and hence all such individuals are entitled to undergo such surgery if they elect to do so after they and their families are fully aware of the fact that no one can predict whether or not any benefit will ensue. It would seem that enough good results, temporary although they may be, have been obtained to justify this stand. It is not the dangers, either immediate or remote, of removing the adrenals that should deter us from using this procedure, but the uncertainty that the ultimate result will be of sufficient benefit to the patient to justify the operation.

ADDENDUM

Of the nine cases being reported, four patients are living at twenty, twelve, nine, and six months, respectively, after adrenalectomy. All, we believe, have shown clinical improvement; also, the patient who died of a ruptured ulcer. The other four are dead and showed no worth-while clinical improvement.

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THE RATIONALE OF ROUTINE OMENTECTOMY IN SUBTOTAL GASTRECTOMY

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INTRODUCTION

THE greater omentum has been the subject of considerable attention through the years, and the accumulated literature is replete with both fact and fancy. Indeed, almost mythical powers have been attributed to the omentum, and its sobriquet, "the policeman of the abdomen,"[11] is frequently heard. Surgeons refer to its alleged supernatural talents in reverent tones. Chief among its powers is thought to be its ability to survive when deprived of its blood supply and its capacity to furnish sustenance to other less fortunate devitalized or devascularized tissues. On the occasions when the omentum is removed by either necessity or design, one often senses a note of anxiety in the surgeon[5] as though he had deprived the patient of his best protection against peritonitis.

As a result of a wide experience with patients undergoing subtotal gastrectomy for carcinoma and peptic ulcer, it was noted that those in the carcinoma group, in whom omentectomy had been performed to provide for a more radical removal of lymph nodes, convalesced more smoothly than the patients in the ulcer group, in whom the omentum had not been resected. This was most striking in obese individuals. Of course, there are other intrinsic technical differences in these two groups, and the most important of these is probably related to the ease of closure of the duodenal stump. But when uncomplicated cases were compared it was obvious that the carcinoma group presented lower postoperative temperature reactions, and achieved a sense of well-being earlier than the ulcer group. Abdominal distention was rarely, if ever, a problem, and stomal difficulties were unusually low in incidence. In the rare instances of peritonitis, the resistance of the patient was entirely unimpaired. As carried out today, the operation of gastric resection is not so much concerned with mortality (less than 1 per cent in many series) as with decreasing the incidence of postoperative morbidity.

In reviewing the anatomic and technical features of the two types of subtotal gastrectomy, it occurred to one of us (P. A. K.)[6] that the essentially avascular attachment of the greater omentum to the transverse colon is a subminimal source of blood supply when the omentum is not removed with the stomach, and that changes in the omentum due to such vascular impairment might well account for the increased morbidity in many instances. The experimental aspects of this paper were designed to prove this hypothesis.

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HISTORICAL REVIEW

In recent years only three authors have dealt with this subject. Fritzsche[2] (1942) observed two instances of postgastrectomy partial necrosis of the omentum at autopsy which he felt contributed to the fatal outcome. He attributed this to ligation of both gastroepiploic arteries while the omentum was left in

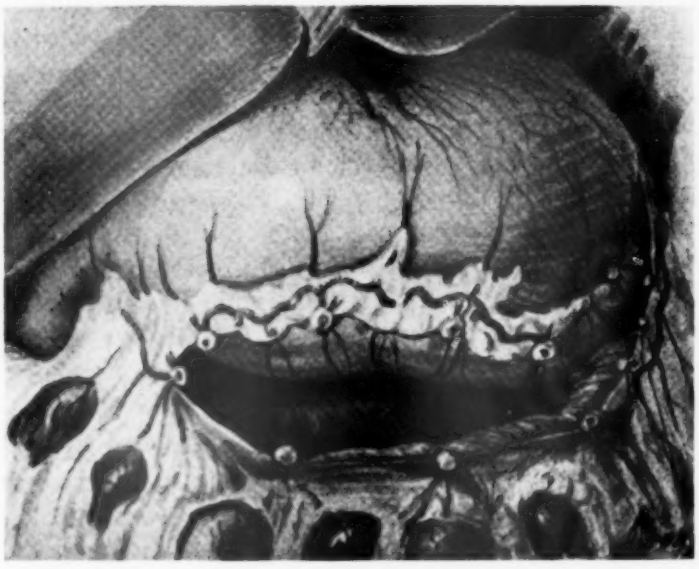

Fig. 1.—Conventional method of mobilization of greater curvature showing compromise of omental circulation by ligation of epiploic vessels outside the epiploic arch. (After Fritzsche.[2])

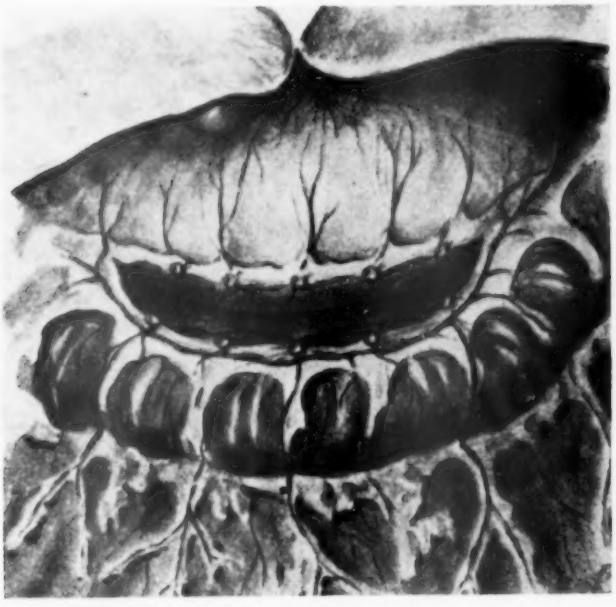

Fig. 2.—Preservation of omental circulation by ligation of gastric vessels inside the epiploic arch. (After Fritzsche.[2])

situ. As a result of careful anatomic and injection studies, he recommended preservation of the omental circulation by ligating the vessels close to the gastric wall inside the epiploic arch (Figs. 1 and 2).

Fig. 3.

Fig. 4.

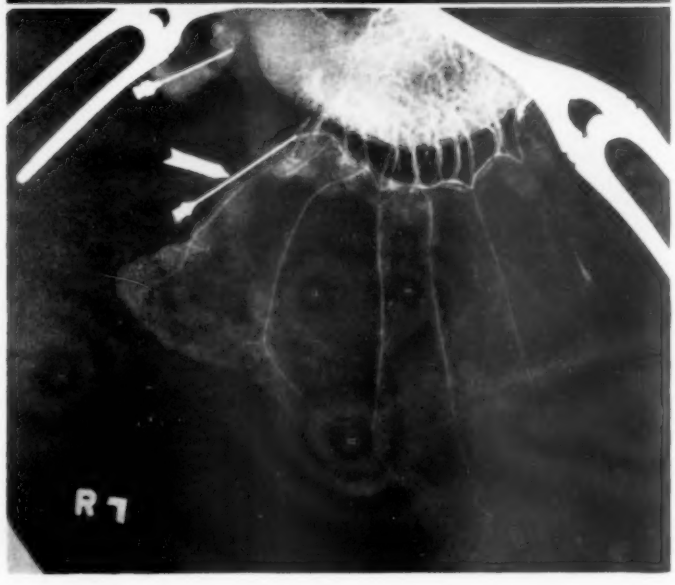

Fig. 3.—Radiograph of injected total gastrectomy specimen showing prominent "oblique artery" (*X*).

Fig. 4.—Radiograph of injected subtotal gastrectomy specimen showing more common arrangement of epiploic vessels.

Lake[7] (1948), in England, apparently unaware of Fritzsche's work, reported six cases of nonfatal omental necrosis, three of which he proved at laparotomy, and considered this a hitherto unobserved complication of sub-

total gastrectomy. He felt that, in lesser degree, this complication occurred often, and related it to interference with the variable blood supply leading to considerable thrombosis within the omentum. No preventive technique was offered.

Horton[5] (1952), in an anatomic study, described the anastomoses between the epiploic branches of the right and left gastroepiploic vessels. He made particular reference to a large branch of the left gastroepiploic artery which runs downward and to the right in the anterior omental leaf. He stated that this "oblique artery" is constantly present and "accounts for the great rarity of sloughing of the omentum after an operation which has apparently destroyed nearly all of its blood supply" (Figs. 3 and 4).

Other authors alluded briefly to this subject in their writings on gastric surgery. Gordon-Taylor, Hudson, Dodds, Warner, and Whitby[3] (1928) described a change in their technique from en masse ligation of omental vessels outside the epiploic arch, to careful individual ligation close to the stomach to preserve as much blood supply as possible. They had not encountered harm from the original ligation method, but they felt that it was irrational. Nario[12] (1934) stressed preservation of the gastroepiploic vein (?arch) in gastric surgery to maintain omental integrity. Wells and Brewer[15] (1948) would sacrifice the omentum if both right and left gastroepiploic vessels were ligated, but considered this an undesirable situation and preferred the method of Gordon-Taylor of preserving the blood supply. Welch[14] (1951) also subscribed to the idea of preserving the epiploic arch, particularly in obese individuals.

Bancroft[1] (1951) and Marshall[10] (1949) advocated omentectomy if they feel that a fatty omentum will interfere with an antecolic gastrojejunostomy. Wangensteen[13] (1952) and Harvey[4] (1940) alluded to omentectomy, but gave no details.

EMBRYOLOGY AND ANATOMY

The greater omentum develops in the embryo from the primitive dorsal mesentery of the stomach (dorsal mesogastrium). The initial changes start at about the fifth week, when the omental bursa begins to form, and progress rapidly thereafter. As the stomach enlarges and then rotates on both sagittal and coronal axes to assume its definitive position, the dorsal mesogastrium enlarges to the left and downward, enclosing within it the space known as the lesser peritoneal sac (omental bursa). The greater omentum assumes the form of a dorsoventrally flattened sac. In the third month, the flat dorsal wall of the sac fuses with the posterior abdominal wall from above downward and progressively adheres to the transverse mesocolon and then the transverse colon itself. Thus, there is no basic vascular relationship between the greater omentum and the transverse colon and mesocolon. Hence, the transverse mesocolon is fundamentally a double leaf composed of four peritoneal layers, and the omental connection between stomach and transverse colon known as the gastrocolic ligament is an embryologically ambiguous term. Further fusion of the dorsal and ventral leaves of the omentum results in a variable degree of obliteration of the inferior recess of the lesser sac, most marked on the right. In the obese adult, the omentum becomes heavily laden with fat.

Aside from the mechanical support of bowel, mesenteries act as a scaffold for intestinal blood supply. In the case of the stomach, the two major sets of vessels in the greater omentum are the right and left gastroepiploic vessels and intervening arch. These run in the anterior leaf, and supply both the stomach and most of the omentum. There is only a meager network in the posterior leaf not related to the adherent transverse mesocolon or colon. This is well demonstrated in the adult when the greater omentum is freed up from the transverse colon and resected with the stomach, as is routinely done in carcinoma cases. An essentially avascular plane of cleavage is entered—often as few as two or three, rarely more than four or five tiny vessels require ligation. These vessels have no relation to the middle colic artery or its branches, but are fine channels derived from the inferior pancreatic artery and course in the posterior leaf of the omentum rather than the mesocolon. Fig. 5 illustrates the paucity of cross-vascular supply from the middle colic artery to the omentum.

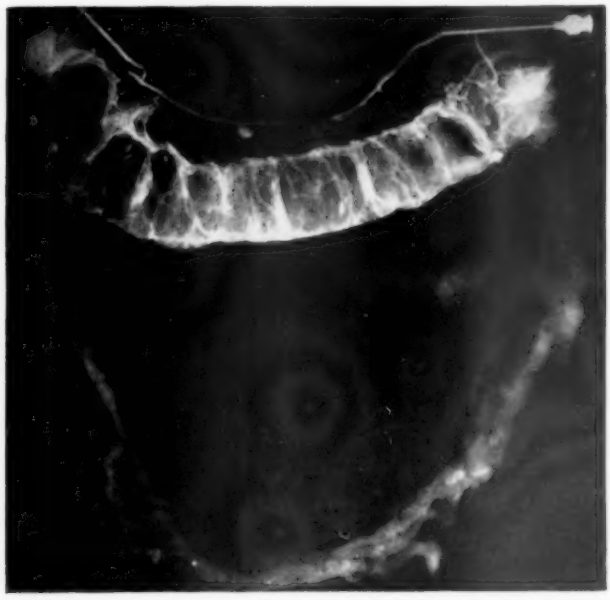

Fig. 5.—Radiograph of cadaver specimen of transverse colon and attached omentum. Injection of middle colic artery fails to visualize omental circulation.

When one considers the blood supply of the omentum itself, one readily notes that practically all of it is derived from the epiploic arch via the anterior leaf. The epiploic arch exists as such mainly on the right two-thirds of the greater curvature, whereas the left one-third is often absent, being replaced by the long epiploic branches of the left gastroepiploic vessels. These right and left epiploic branches supply the entire anterior leaf and the majority of the posterior leaf with the exception of the meager vascularity described previously. It is this rich blood supply which is ablated in the standard gastric resection for benign lesions when the omentum is not removed with the stomach and the integrity of the epiploic arch is not deliberately preserved.

EXPERIMENTAL OBSERVATIONS

Anatomic Studies.—Cadaver material and surgical specimens (both total and subtotal gastrectomy) were utilized for gross anatomic studies. The vascular pattern of the omentum was clearly demonstrated by injecting 10 to 15 c.c. of warmed iodized oil (Iodochlorol) into the cannulated right gastroepiploic artery. The minute vessels are as easily demonstrated by this method as the major trunks. In specimens in which the stomach was not detached from the omentum, the rich intramural gastric blood supply was well pictured, even to the filling of the lesser curvature vessels (Figs. 3 and 4).

The vascular distribution of the omentum follows a fairly standard pattern. From the convexity of the epiploic arch, a series of large vessels (eight to twelve) arises and courses downward. There are some anastomoses between these vessels, mainly near the inferior margin of the omentum. A few finer connections occur closer to the arch. The vessels run in the interlacing columns of fatty tissue, and the thin transparent layers between these columns are devoid of large channels. Although one of the specimens (Fig. 3), a total gastrectomy and splenectomy for carcinoma, demonstrated a prominent oblique artery, this vessel was by no means a constant finding.

A special preparation was made of a cadaver specimen in which the omentum was removed from the stomach but left adherent to the transverse colon. Injection of the middle colic artery showed only a minute scant tracery that could be construed as being in the omentum (Fig. 5). The reason for this has been given in the section on embryology and anatomy.

Animal Experiments.—Since we had no clinical material of sufficient importance to validate our original hypothesis, a series of experiments was devised to simulate the conditions found in the human being. Mongrel dogs weighing 10 to 18 kilograms were used. All operations were carried out under intravenous Nembutal anesthesia with strict aseptic technique. Normally these dogs present a thin delicate transparent lacelike omentum (Fig. 6) in which the lesser sac has not become obliterated. The posterior leaf is not fused with the transverse colon as in man, but arises from the posterior abdominal wall and encloses within it part of the pancreas. The epiploic arch and its branches are analogous to those in man, and the oblique artery of Horton is constant, being the major epiploic branch of the left gastroepiploic artery. The latter vessel in turn is derived from the inferior branch of the splenic artery. In the posterior leaf there is a series of four or five small-caliber vessels analogous to the fine bleeding points noted in man when the omentum is shaved off the transverse colon.

The so-called oblique artery was so constant in dogs that it was utilized in most of the experiments as the residual source of blood supply after ablation of the epiploic arch and branches (Fig. 7). In eight dogs the right gastroepiploic artery and the epiploic branches of the arch were ligated, leaving the omentum attached only by the oblique vessels, the posterior leaf alone, or a combination of the two. Gastrectomy was not performed. Great care was

Fig. 6.

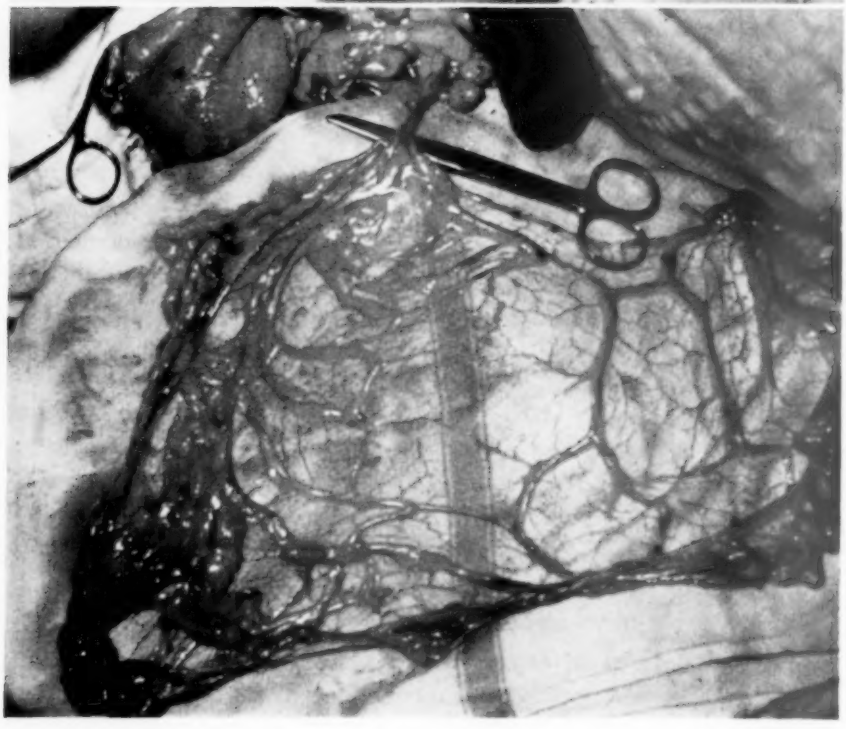

Fig. 7.

Fig. 6.—Omentum, stomach, and spleen of dog. Clamp points to right gastroepiploic artery.

Fig. 7.—Experimental situation: subtotal devascularization of dog's omentum, only source of blood supply from oblique artery (left epiploic).

taken in handling the delicate omentum. In spite of this, some hemorrhagic and ecchymotic areas appeared. Observations were made at intervals of two to twenty-four days.

The characteristic gross change was the conversion of all or a good part of the omentum into a solid mass—heavy, soggy, indurated, of a mottled yellowish brown color, and usually nonadherent to surrounding loops of bowel (Figs. 8 and 9). This "tumor" was easily palpated through the abdominal wall. After the second day, there was no free peritoneal fluid. No evidence of infection was present. The mass was obviously viable, and except for one animal in which a moderate amount of trauma and hemorrhage into the omentum had occurred because of handling, there was no resemblance to hemorrhagic infarction of the omentum. The cut surface appeared more succulent and edematous in the earlier specimens, but drier and more resistant to incision later (Fig. 10). This change was due to increased fibrosis. The vessels of the pedicle and on the surface of the mass were not thrombosed.

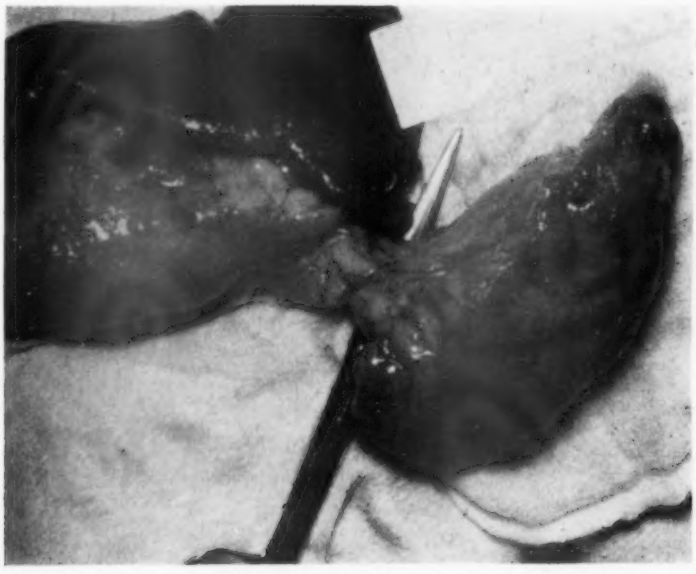

Fig. 8.—Omental "tumor" seven days later.

Microscopically the changes paralleled the gross findings. In the two- to seven-day group, the fat cells appeared turgid, and the cell membranes were of compromised viability (Figs. 11 through 14). There was a considerable degree of intercellular edema, extravasation of red blood cells, collections of polymorphonuclear leukocytes in the form of microabscesses, and the appearance of young granulation tissue. In the second and third weeks, more mature fibrous tissue made its appearance along with some foreign-body giant cells, the latter possibly related to suture material. In no specimen was there any evidence of vascular thrombosis or hemorrhagic infarction. There was a tendency for the necrotic fat cells to rupture, coalesce, and form larger spaces bounded by thin layers of fibroblastic tissue (Fig. 15).

In general the changes were those of early sterile inflammation and fat necrosis progressing to later fibrosis and repair. Infection was not a factor in these alterations. The resemblance to the so-called inflammatory tumors of the omentum as described by Lewisohn[9] (1923) and others was striking.

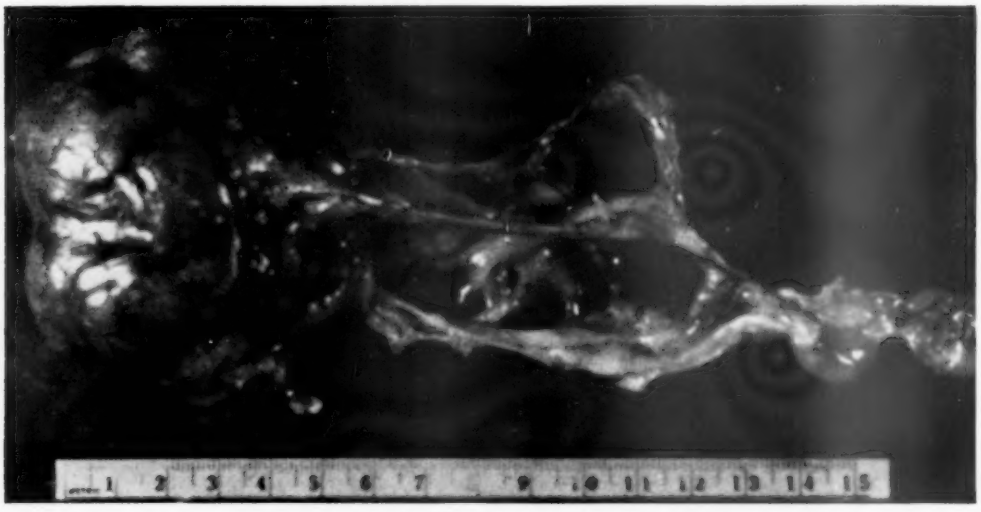

Fig. 9.—Omental tumor at five days showing intact vascular pedicle.

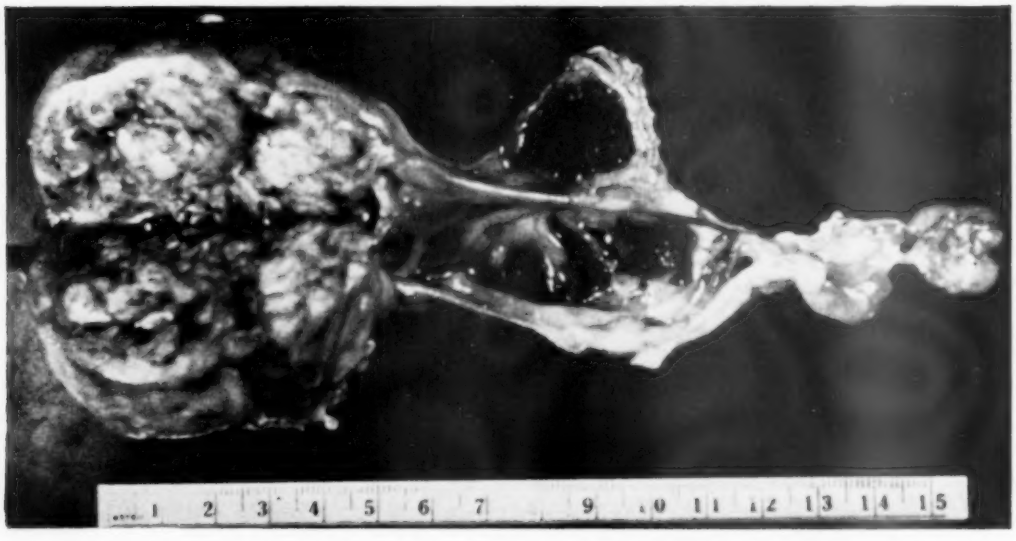

Fig. 10.—Cut surface of specimen shown in Fig. 9.

Two special experiments were carried out to help clarify these observations. In one animal the right gastroepiploic artery was ligated, and the gastric branches of the epiploic arch were ligated and divided (after the method of Gordon-Taylor and associates), leaving an intact pulsating epiploic arch. As might be expected, no changes were observed in the omentum after six days.

In another animal the omentum was completely detached outside the epiploic arch, and the free mass was then dropped back into the peritoneal cavity. Thirteen days later the animal was re-explored. The peritoneal cavity

Fig. 11.

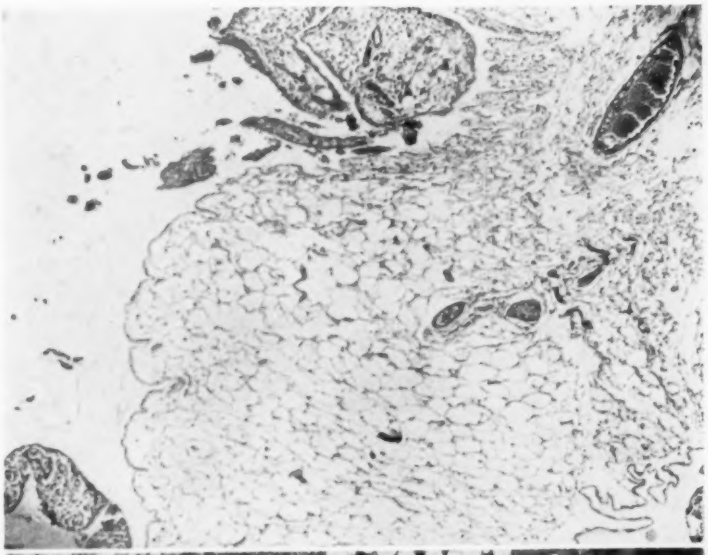

Fig. 12.

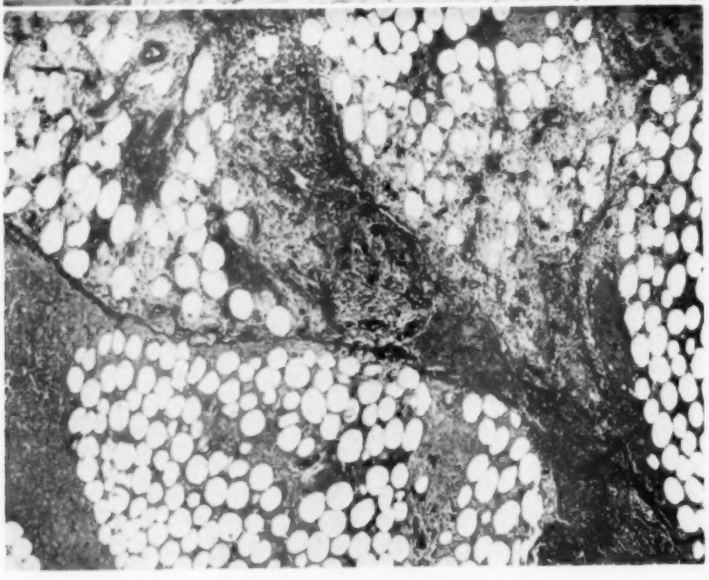

Fig. 11.—Photomicrograph of normal dog omentum.

Fig. 12.—Photomicrograph of omental tumor of dog at two days showing intercellular edema, cellular infiltration, and fat necrosis.

contained about 50 c.c. of clear, colorless oily fluid. The detached omentum had become adherent to two loops of small bowel, and the splenic hilum. It had a peculiar "dead-white" color with a faint yellowish tinge. The fatty portions disintegrated on light touch and felt very soft. A stroma of strand-

like material, probably the remnants of blood vessels, was clearly visible. A loop of engulfing bowel with adherent omentum was resected. Microscopic sections showed that the serosa of the bowel had been the source of new blood

Fig. 13.

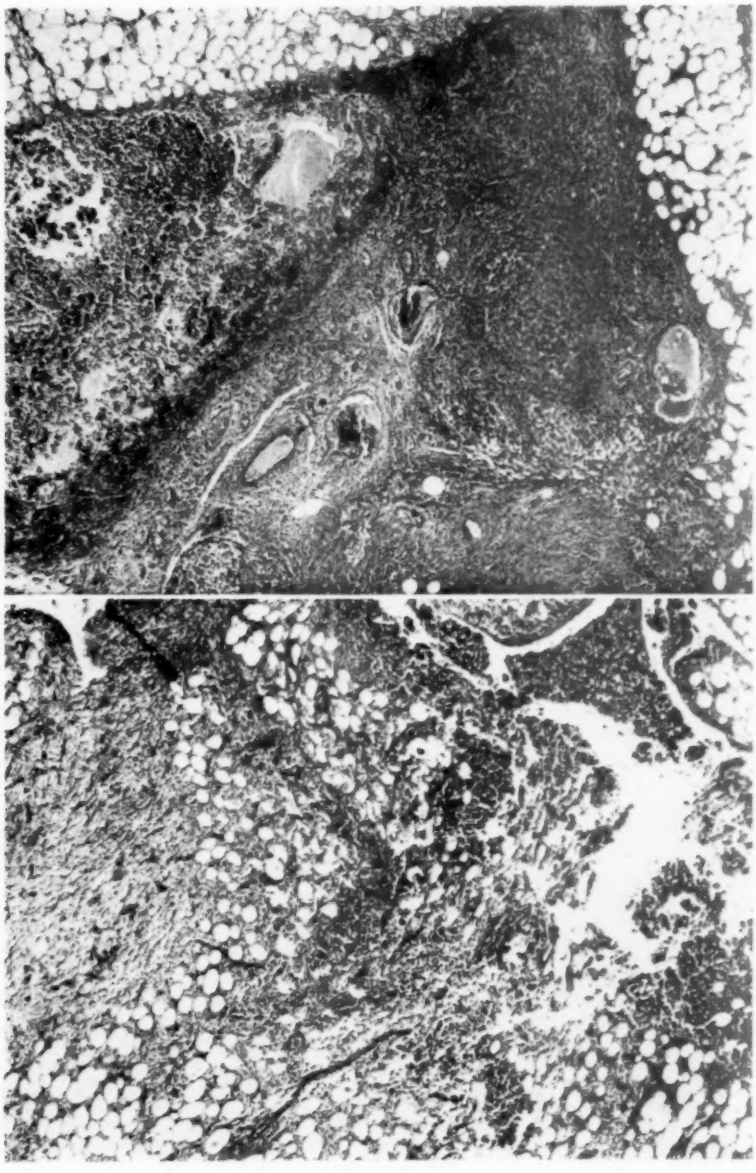

Fig. 14.

Fig. 13.—Five-day specimen showing granulation tissue and microabscess (upper left).
Fig. 14.—Another portion of a five-day specimen showing more mature granulation tissue and fibroblasts.

supply (Fig. 16). There was an outgrowth of blood vessels from the bowel wall into the omentum. Large vacuole-like spaces were present—the remnants of ruptured fat cells. The interstitial tissue was of a fairly mature fibrous nature, although much more delicate than in the partially devitalized omentum

of the original experiments. Very little resemblance to normal omentum could be made out. Aside from these objective findings, one might speculate as to the fate of free omental grafts—that they receive rather than furnish sustenance and support from adjacent tissues.

Fig. 15.

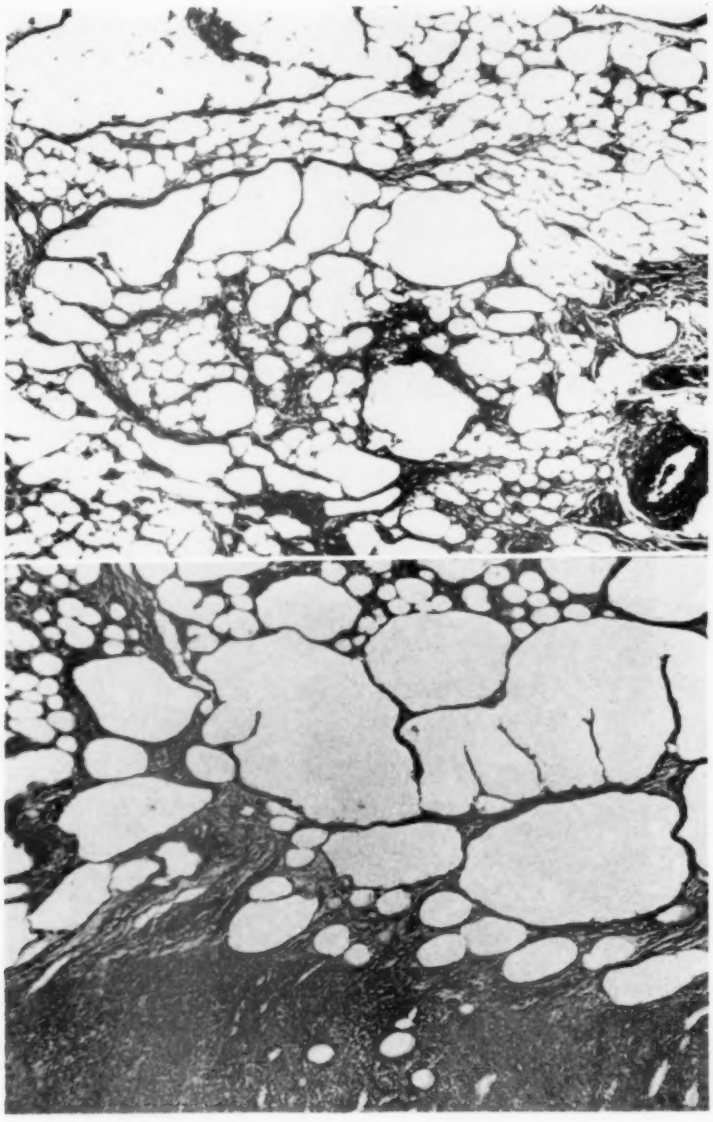

Fig. 16.

Fig. 15.—Twenty-four-day specimen showing coalescence of ruptured fat cells to form large vacuoles, more mature fibrous tissue, and disappearance of inflammatory elements.

Fig. 16.—Completely freed omentum which has become adherent to loop of small bowel at thirteen days showing outgrowth of vessels from bowel wall (bottom) into omentum. Note resemblance of omentum proper to subtotally devascularized specimen in Fig. 15.

One other observation was made. In one dog the usual partial devascularization was carried out. Nine days later, a mass was present consisting of the omental tumor walling off an abscess between itself and the under-

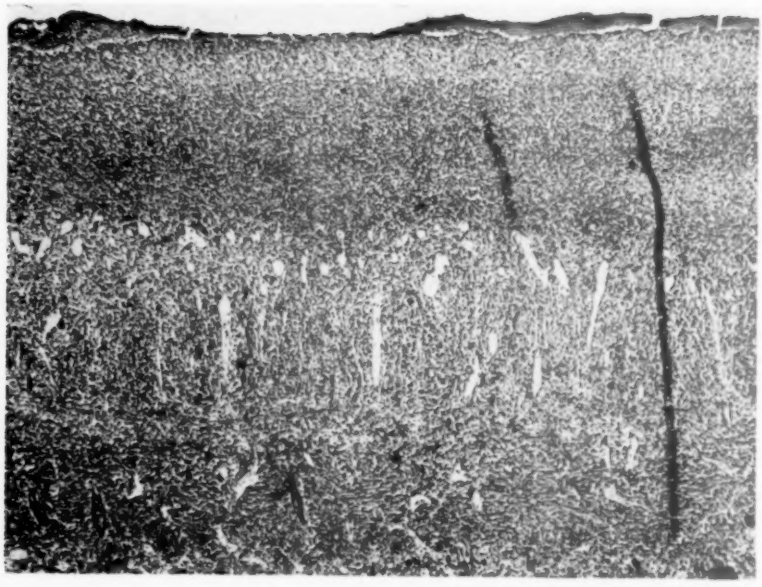

Fig. 17.—Splenic wall of abscess (nine days) showing rich granulation tissue response and pyogenic membrane.

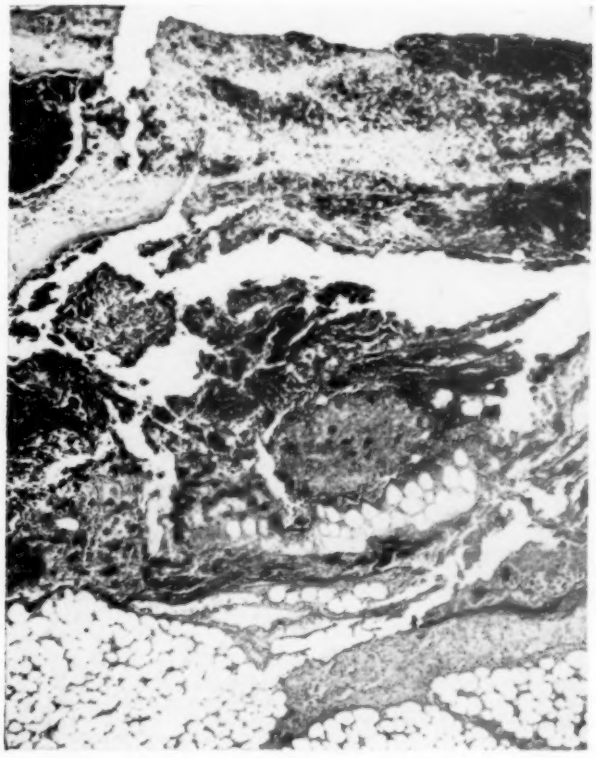

Fig. 18.—Omental wall of same abscess showing only colonies of bacteria and fat necrosis. No active tissue response is seen.

surface of the spleen. Sections of the wall of the abscess showed a striking finding; namely, that on the splenic side (Fig. 17) a true pyogenic membrane and vascular granulation tissue barrier had been laid down, whereas on the omental side (Fig. 18) no attempt at granulation tissue was seen. This lack of contribution by the devascularized omentum of a tissue reaction to infection suggests the dubious value of such omentum as a protection against peritonitis.

SUMMARY AND CONCLUSIONS

An experimental study has been carried out to determine the changes occurring in the partially devascularized omentum after the standard subtotal gastrectomy for duodenal ulcer.

Evidence of a theoretical and experimental nature has been advanced to suggest that omentectomy should be carried out routinely in all cases of subtotal gastrectomy for whatever cause. Removal of such omentum does not deprive the patient of the "policeman of the abdomen" but may well rid him of a noxious mass of fatty tissue undergoing sterile inflammation, necrosis, absorption, and organization. The technique of removal is simple and bloodless, and is based upon sound anatomic and embryologic principles. Removal is less tedious than preservation of the epiploic circulation, although that procedure would accomplish the same purpose. Omentectomy should find its best application in the obese individual where the opportunity for fat necrosis is greatly increased.

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A STUDY OF THE CAPILLARIES OF THE GASTRIC MUCOSA

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IN DECEMBER, 1951, Barlow, Bentley, and Walder,[1] of Kings College, University of Durham, England, reported a functional shunt in the blood vessels of the gastric mucosa. These workers were able to demonstrate, by perfusion experiments with different sized tiny glass beads and by radiophotomicroscopy, that the gastric mucosal capillary network is supplied with blood when the vessels of the shunt are closed and that there is relative mucosal ischemia when the shunts are open.

Such a mechanism is comparable to the findings of Trueta and his coworkers[2] in the kidney and to Zweifach's[3] concept of the basic capillary functional unit present, with variations, throughout the body and consisting of a capillary network and shunts. When the local area is at rest, the shunts are open; they close when the tissues involved need more blood. This concept is diagrammatically represented in Fig. 1.

It is of interest to note that Zweifach's work, which was based primarily upon a study of the muscular coats of blood vessels, has been confirmed by the majority of investigators of the capillaries and is supported by Nelemans'[4] study of nerve filament supply to small blood vessels. The nerve distribution is comparable to that of the muscle.

Barlow and associates[1] in 1951 also submitted evidence that stimulation of the vagus nerves resulted in closure of the shunts (nonpassage of the larger pellets) and hyperemia of the capillary bed (demonstrated by radiophotomicroscopy). The opposite result occurred with sympathetic stimulation.

If it is true that stimulation of the vagus nerves causes gastric mucosal hyperemia and that vagus hyperactivity is associated with hyperacidity and chronic ulcerative disease of the stomach and duodenum, in patients with peptic ulcer one should expect to find capillary congestion of the gastric mucous membrane over and above that associated with any incidental inflammatory process.

With this premise in mind, fifty cases were selected from the files of the Department of Pathology of the University Hospital. These cases were divided approximately evenly between patients who had had total or partial gastrectomy for ulcerative or nonulcerative disease. The routine microscopic sections of these stomachs were reviewed without knowledge of the diagnoses. Capillary counts were made in an area of the gastric fundus well removed from the region of disease.

The technique employed for the counts was as follows. No special stains were employed. Capillaries were identified in the mucosa as vessels with diameters not greater than that of three red blood cells, and care was taken to eliminate, as much as possible, recounting vessels cut in a longitudinal plane.

The field provided by a 43× objective (4 mm. focal length) and a 10× ocular on a standard monocular microscope with tube length of 160 mm. was calibrated

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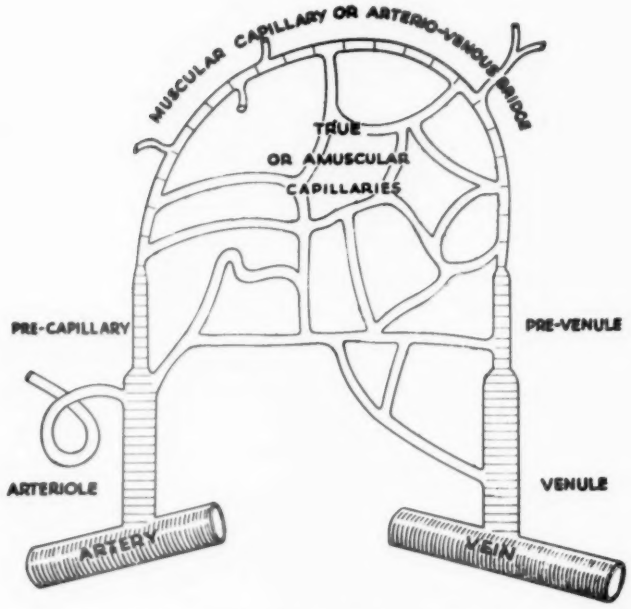

Fig. 1.—Zweifach's concept of the basic capillary functional unit.

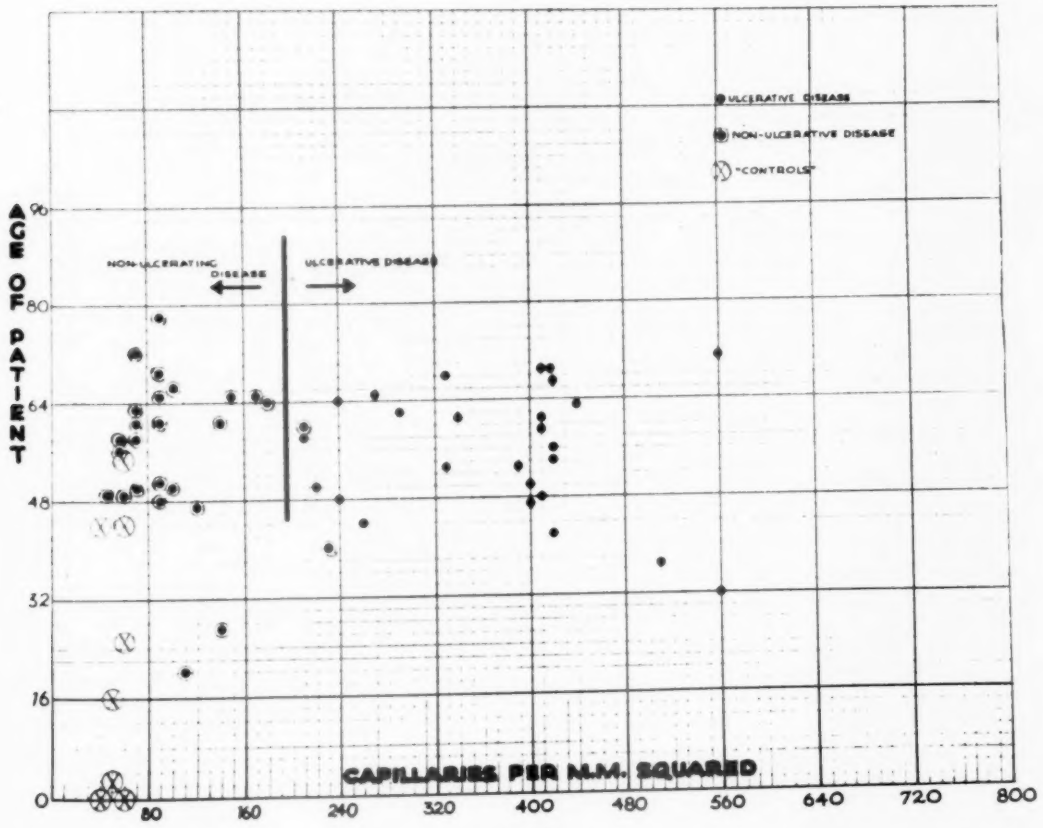

Fig. 2.

TABLE I.

PATH. NO.	HOSP. NO.	DIAGNOSIS	AGE (YR.)	CAPILLARY COUNT PER SQUARE MILLIMETER
1—3160—BD	715738	Gastric ulcer and chronic atrophic catarrhal gastritis	71	560
2—4946—BB	606220	Duodenal ulcer; chronic hypertrophic catarrhal gastritis	32	560
3—8468—BB	681801	Duodenal ulcer; chronic hypertrophic catarrhal gastritis	37	510
4—3140—BD	715944	Gastric ulcer; chronic catarrhal gastritis	63	440
5—5238—BB	216539	Duodenal ulcer	42	420
6—1878—BB	468438	Duodenal ulcer	67	420
7—2702—BD	650508	Duodenal ulcer; chronic atrophic and hypertrophic catarrhal gastritis	54	420
8—5128—BB	672680	Duodenal ulcer; chronic hypertrophic catarrhal gastritis	58	420
9—3282—BD	713974	Duodenal ulcer; chronic atrophic and hypertrophic catarrhal gastritis	48	410
10—1228—BD	459459	Gastric ulcer; chronic hypertrophic catarrhal gastritis		410
11—2009—BD	695305	Gastric ulcer; chronic hypertrophic catarrhal gastritis	59	410
12—439—BD	708427	Ulcerating adenocarcinoma of stomach and chronic catarrhal inflammation	69	410
13—1870—BB	667148	Duodenal ulcer; chronic catarrhal gastritis	61	410
14—2185—BD	288244	Gastric ulcer; hypertrophic catarrhal gastritis	50	400
15—8154—BB	679900	Duodenal ulcer; chronic catarrhal gastritis	47	400
16—2360—BD	701829	Gastric ulcer; chronic hypertrophic catarrhal gastritis	53	390
17—1785—BD	712874	Gastric ulcer; active chronic atrophic gastritis	61	340
18—1173—BD	663111	Gastric ulcer; chronic catarrhal gastritis	68	330
19—2360—BD	701829	Duodenal ulcer; chronic hypertrophic catarrhal gastritis	53	330
20—3388—BD	715823	Duodenal ulcer; chronic hypertrophic catarrhal gastritis	62	290
21—4257—AW	563856	Gastric ulcer in region of lymphosarcoma	65	270
22—2936—BD	502156	Duodenal ulcer; chronic hypertrophic catarrhal gastritis	44	260
23—2332—AU	513117	Gastric ulcer; lymphoblastoma of stomach; chronic hyperplastic gastritis	48	240
24—2287—BA	641919	Neurofibroma of stomach; chronic catarrhal gastritis	64	240
25—5167—AU	522738	Scirrhous carcinoma, Grade III, of stomach; hyperplastic catarrhal gastritis	40	230
26—1712—AU	511764	Lymphosarcoma of stomach; chronic gastritis	50	220
27—515—AR	446791	Lymphosarcoma with large area of ulceration	60	210
28—1184—BD	574124	Duodenal ulcer; chronic hypertrophic catarrhal gastritis	58	210
29—2761—BA	287333	Adenocarcinoma of stomach; atrophic gastritis	64	180

TABLE I. CONT'D

PATH. NO.	HOSP. NO.	DIAGNOSIS	AGE (YR.)	COUNT PER CAPILLARY SQUARE MILLIMETER
30—753—BD	708731	Adenocarcinoma of stomach; chronic atrophic catarrhal gastritis	65	170
31—147—BD	707581	Medullary carcinoma of stomach	65	170
32—4946—AZ	629833	Leiomyoma of stomach	27	140
33—12—AR	445974	Adenocarcinoma of stomach	61	140
34—3579—AU	518216	Scirrhous carcinoma of stomach	47	120
35—6084—BB	659129	Carcinoid of stomach; chronic catarrhal gastritis	20	110
36—1080—AW	551364	Neurofibroma of stomach	66	100
37—4647—AU	521657	Scirrhous carcinoma of stomach; catarrhal gastritis	50	100
38—650—AX	572636	Adenocarcinoma of stomach; catarrhal gastritis	70	100
39—3299—BD	635105	Lipoma of stomach; chronic hypertrophic catarrhal gastritis	65	90
40—4187—AU	520036	Adenocarcinoma of stomach; marked hypertrophic catarrhal gastritis	61	90
41—4218—AU	519511	Adenomatous hyperplasia of Brunner's glands; hyperplastic catarrhal gastritis	48	90
42—378—AU	507257	Lymphosarcoma of stomach; hyperplastic catarrhal gastritis	51	90
43—151—AV	441647	Lymphoblastoma of stomach	69	90
44—3489—AY	605695	Lymphoblastoma of stomach	78	90
45—1436—BD	709686	Adenocarcinoma of stomach; chronic atrophic catarrhal gastritis	72	70
46—7875—BC	703331	Lymphosarcoma of stomach	50	70
47—824—AV	531223	Adenocarcinoma of stomach	63	70
48—6114—AU	527107	Adenocarcinoma of stomach	61	70
49—3827—AU	518155	Carcinoma of stomach; catarrhal gastritis	58	60
50—4716—AU	521472	Adenocarcinoma of stomach; chronic catarrhal gastritis	56	60
51—6197—AU	526805	Adenocarcinoma of stomach; hypertrophic catarrhal gastritis	59	60
52—1654—AX	394945	Gastric polyp, benign; chronic catarrhal gastritis	49	50

by replacing the microscopic section with a blood-counting chamber. It was possible to take counts in rectangular fields of various sizes from 0.2 sq. mm. to 0.8 sq. mm. Counts were made of five representative fields from each stomach and the results converted to capillaries per square millimeter. It is realized that the figures are semiquantitative only; however, they should be comparable from case to case. All examinations were made on operative material, in order to secure comparable blood content, so far as possible. Having determined the capillary counts per square millimeter for each stomach, various correlations were attempted, which are represented in the accompanying graphs and tabulations.

The following results were secured. Cases are arranged in descending order of capillary counts.

It was felt wise to carry out some measure of control of the counts shown in Table I. This was done, and in five instances slides were recounted without knowing the case at hand. The results of these recounts are as follows:

CASE NO. IN TABLE I	ORIGINAL COUNT	REPEAT COUNT	APPROXIMATE % OF VARIATION
13	410	390	5
19	330	390	15
7	420	400	5
28	210	220	5
45	70	50	30

The approximate average variation of rechecked counts was 12 per cent, which may not be important in view of the semiquantitative nature of the method and considering that if counts in all cases of ulcerative disease were lowered 12 per cent and in the nonulcerative cases raised 12 per cent, there would still be a good point of demarcation between the two groups.

In addition to the recounts, an effort was made to find some "normal" stomach sections in necropsy material. Those selected were as follows:

PATH. NO.	HOSP. NO.	AGE (YR.)	CASE	DIAGNOSIS OF STOMACH	COUNT
A-467-BA	649471	16	Cardiac arrest on operating room table; operation for congenital polyposis of colon	No microscopic evidence of abnormality of stomach	50
A-269-BD	642787	25	Cardiac arrest during pulmonary lobectomy	Congestion of submucosal vessels; does not involve mucosal capillaries	60
A-245-BD	719423	56	Cardiac arrest during cystoscopy	Slight post-mortem change; congestion of submucosal vessels	60
A-233-BC	691212	3	Leukemia; autopsy 30 min. following death	Slight leukemic infiltration and post-mortem change	50

Routine teaching slides from sets in the laboratory of histology were also counted. Slide 1893 of the stomach of a term fetus contained 50 capillaries per square millimeter, as did Slide 1090 from the stomach of an adult. These histologic slides on several recounts gave a spread of from 40 to 60 capillaries per square millimeter.

The tabulations are presented graphically in Fig. 2 by plotting the count against the age of the patient. Cases of ulcerative disease are noted by solid points, those of nonulcerative disease by circles, and the "controls" by circles enclosing crosses.

CONCLUSION

It seems reasonable to conclude from the data presented that there is greater hyperemia in the capillaries of the gastric mucosa of patients with ulcerative disease of the stomach and duodenum than in cases of malignancy, nonulcerative disease, and in "normal" stomachs.

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FATAL COMPLICATIONS AFTER ESOPHAGEAL REPLACEMENT WITH PLASTIC TUBE

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IN THE past one and one-half decades, cancer of the esophagus has been progressively attacked from the lower third up to and including the supra-aortic and cervical portions. While the five-year survival rate for the lower third neoplasms has encouraged surgeons, the high surgical mortality and extremely low five-year survival rate for retro- and supra-aortic esophageal cancer has spurred investigators to search for a safer and more simple technique.

Berman[1] utilized a plastic polyethylene tube to bridge the esophageal defect in dogs, and Moore[5] repeated this work utilizing rabbits. Their follow-up studies indicated that the fibrous sheath encasing the tube became lined with squamous epithelium, restoring esophageal continuity and permitting satisfactory alimentation. This procedure has been carried out in a series of sixty patients[2, 3] with satisfactory palliation.

Our recent experience utilizing similar plastic tubes to restore esophageal continuity in two patients following wide local resection merits publication to demonstrate both an early and late fatal complication that might be avoidable.

Case 1.—A 71-year-old white woman was admitted in November, 1953, with the chief complaint of substernal burning and progressive dysphagia of three weeks' duration. A barium esophagram demonstrated a large obstructing lesion of the esophagus extending from the aortic arch inferiorly to the esophagogastric junction. Relevant past history revealed that the patient had a one-stage resection of a cecal adenocarcinoma in 1951 without subsequent recurrence as demonstrated by abdominal examination and roentgen study. The advanced age, borderline cardiac reserve, and history of previous gastrointestinal carcinoma precluded radical surgery. To achieve palliation, a resection of the lower half of the esophagus with insertion of a plastic tube through the left thoracotomy incision, utilizing the bed of the seventh rib, was carried out. Pathologic report of the excised specimen revealed squamous cell carcinoma, Grade II, with lymph node metastases. The patient remained afebrile during the postoperative course. Peristalsis on the third day was followed by flatus and bowel movements on the fourth postoperative day. No abdominal distention was noted, and left thoracotomy tube drainage was predominantly serosanguineous and scanty until death. Serial postoperative chest films indicated some loculated fluid in the left posterior chest. On the sixth postoperative day, sudden onset of auricular fibrillation was followed by cardiac failure, peripheral vascular collapse, and oliguria, and the patient expired within twenty hours.

At post-mortem, 1,500 c.c. of muddy, greenish fluid in the left thorax was revealed as the cause of atelectasis of the left lung. This fluid was also present in the mediastinum and dilated atonic stomach. Silk purse-string sutures fixing the plastic tube to both ends of the esophagus were intact. There was no evidence of residual or metastatic esophageal cancer, and no intra-abdominal cancer related to previous cecal neoplasm was observed.

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Comment.—The indication for use of plastic tube in this instance was recent separate primary carcinoma together with borderline cardiac reserve in an elderly, obese patient. A nasogastric tube for decompression was not utilized in an effort to minimize the pharyngeal irritation, secretions, and attendant pulmonary complications. Furthermore, when peristalsis, flatus, and feces were noted in the early postoperative period without nausea, vomiting, epigastric fullness, or substernal distress, we felt encouraged to believe that this decision was wise. The sudden and rapid cardiovascular deterioration followed by death was unexplained until post-mortem examination, which revealed that this patient had gastric dilatation and atony, with pylorospasm probably induced by bilateral complete vagal section following esophageal resection. Furthermore, since the silk purse-string suture occlusion of the plastic tube to the esophagus was not watertight (to prevent tissue necrosis), the accumulated gastric secretions overflowed into the mediastinum and connecting left pleural space. Cardiac fibrillation, vascular collapse, and oliguria were undoubtedly induced by the mediastinitis. Therefore, it would appear desirable to utilize nasogastric suction for decompression after esophageal (and bilateral vagal nerve) resection until gastric motility and patency of the pylorus are assured.

Case 2.—A 58-year-old man was readmitted to the hospital one month after interstitial radium needle therapy for squamous cell carcinoma of the floor of the mouth without metastatic cervical nodes. A 30-pound weight loss, progressive dysphagia, and debility had been noted since completion of radium therapy. Barium esophogram demonstrated an intraluminal, annular, obstructing mid-esophageal lesion, which was biopsied 30 cm. from the upper incisor teeth and reported as squamous carcinoma, Grade II. Marked debility and weight loss, coupled with a history of the recent intraoral primary cancer and a gastroenterostomy performed ten years previously for obstructing duodenal ulcer precluded a radical surgical attack on this new and separate primary esophageal cancer. The patient was accordingly started on a course of deep x-ray therapy and parenteral fluids. After seven x-ray treatments, intractable hiccoughs and a debilitating cough from puddling of pharyngeal secretions interdicted further use of this modality. Since the pre-existing gastrojejeunostomy precluded use of the stomach for a high esophagogastric anastomosis, a plastic polyethylene tube was inserted to restore esophageal continuity after 8 cm. of esophagus with adjacent nodes and areolar tissue was resected through the bed of the right eighth rib. Pathologic report of the excised specimen was squamous carcinoma, Grade II, without regional node metastases. A satisfactory postoperative course without nasogastric tube suction permitted oral feedings to be started on the third postoperative day, and the patient was discharged on the sixteenth postoperative day on a six-feeding bland diet. A postoperative barium study revealed rapid flow of barium through the tube with some minimal flow around the tube.

Follow-up examinations indicated excellent palliation, with gain in weight and strength; dysphagia was absent. One episode of right lower lobe pneumonitis was controlled by antibiotic therapy. The patient did well until December, 1953, five months after surgery, when a sudden and uncontrolled gastric hemorrhage resulted in death within twenty-four hours. It was our ante-mortem impression that this patient had a fatal hematemesis from a reactivated duodenal ulcer.

At post-mortem, however, an 8 mm. opening in the descending thoracic aorta was found adjacent to the upper end of the plastic tube, which was lying loosely and obliquely within the fibrous sheath. This aortic rent was adherent to and continuous with this esophageal sheath, thus accounting for the fatal hematemesis. There was no evidence of residual or metastatic carcinoma from either the esophageal or floor of the mouth primary cancers.

Furthermore, there was no reactivation of the old duodenal ulcer or evidence of mediastinal infection. Microscopic studies demonstrated that the fibrous sheath was lined by squamous epithelium.

Comment.—In the absence of infection or residual carcinoma in the mediastinum, a foreign body (the plastic polyethylene tube) lying loosely adjacent to a pulsating aorta is incriminated as the source of this fatal hemorrhage. It is also of interest that barium flowed through and around the plastic tube on the sixteenth postoperative day without adverse effects, suggesting that the mediastinal pleura and lung had adequately sealed off the operative bed. It is probable that if this plastic tube had been removed, once satisfactory mediastinal continuity was established, this fatality may have been avoided. Incidentally, failure to employ nasogastric suction in this case did not result in gastric dilatation, probably because of the functioning, antecedent gastroenterostomy.

DISCUSSION

Technical variations of established operative procedures may pose new problems until sufficient clinical trial and experience demonstrate the avoidable pitfalls, particularly in the utilization of synthetic materials to replace living tissue. Experience with the Vitallium tubes to bridge vein and common duct defects and the use of tantalum mesh for support of tissues bear this out. Since retro- and supra-aortic esophageal neoplasms are associated with a high mortality and morbidity and extremely low salvage, sleeve resection of the obstructing esophageal lesion with substitution by a synthetic tube appears worthy of trial. In addition to the two postoperative complications described here, a recent report[4] indicates that recurrent cancer has been noted in the lining of the mediastinal sheath surrounding the plastic tube. It is of incidental interest that both of our patients had double primary carcinomas. We hope that other surgeons will report on their experience with this substitution technique in an effort to evaluate the merit of this procedure.

SUMMARY

1. The use of intrathoracic plastic polyethylene tubes to restore esophageal continuity after resection for carcinoma appears to offer significant palliation.

2. Postoperative nasogastric suction and decompression are recommended to prevent gastric dilatation, atony, and potential mediastinal reflux.

3. Endoscopic removal of the esophageal plastic tube is indicated once healing is complete and continuity is demonstrated by barium esophagram, particularly if the synthetic tube is lying loosely within the mediastinal sheath.

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EXTRINSIC DEFORMITIES OF THE COLON MIMICKING CARCINOMA

A Report of Three Cases

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A VARIETY of conditions may simulate carcinoma of the colon, and extrinsic lesions comprise an interesting group. Pendergrass[34] and others[18] have described the roentgenographic characteristics of the common lesions which generally do not constitute a problem in diagnosis. There are, however, certain rare disorders producing extrinsic constriction of the large intestine, the symptoms and roentgenographic appearance of which may be indistinguishable from the constriction produced by carcinoma. It is the purpose of this communication to report three cases of benign extrinsic lesions of the colon erroneously diagnosed preoperatively as carcinoma, and to review the pertinent features of the less common extrinsic lesions that may present problems in the diagnosis of disorders of the large intestine.

CASE REPORTS

Case 1.—(No. 539020) J. C., a 72-year-old white man, was admitted to the hospital on April 9, 1953. He had been well until four months before admission, when he experienced bouts of cramping abdominal pain with associated anorexia. Bright red bleeding per rectum had been noticed on several occasions in the preceding months. There was a 15-pound weight loss.

The only positive physical findings were those of tenderness in the left lower abdominal quadrant and a moderately enlarged prostate. Laboratory findings were within normal limits. Proctoscopic examination was negative to 25 cm.

Roentgenographic examination with a barium enema on April 15, 1953, revealed an annular lesion in the transverse colon which was believed to be carcinoma (Fig. 1). April 23, 1953, the narrowed segment of transverse colon was again demonstrated by barium enema, and difficulty was encountered in forcing barium proximal to the lesion.

At operation on April 30, 1953, the distal transverse colon was constricted by an epiploic appendix which extended across the antimesenteric border and attached to the gastrocolic ligament. Division of this appendix between clamps readily released the constriction. The patient's postoperative course was uneventful and, following a transurethral resection, he was discharged on May 30, 1953.

Case 2.—C. P. H., a 42-year-old white man, was admitted to the hospital on Dec. 8, 1953, complaining of intermittent episodes of diarrhea for several years. There had been persistent diarrhea and a 12-pound weight loss in the previous three months. Ten days prior to admission the patient developed abdominal pain and passed a tarry stool.

Physical examination revealed only moderate generalized abdominal tenderness. Laboratory studies, including repeated stool examinations, were within normal limits.

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Radiographic studies (Dec. 10, 1953) with a barium enema revealed a defect of the mid-transverse colon that had the appearance of a sessile lesion projecting into the lumen, with a possible ulcer crater in its center (Fig. 2). The radiologist was of the opinion that the defect represented a carcinoma of the colon. On Dec. 17, 1953, a repeat barium enema with air contrast again demonstrated the narrowed area of the proximal transverse colon (Fig. 3). At operation on Dec. 28, 1953, no abnormalities were noted except for adherence of an epiploic appendix across the mid-transverse colon to the gastrocolic ligament, producing constriction and partial obstruction of the colon at this point. There was slight dilatation of the bowel proximal to the site of constriction, and hyperactive peristalsis was noted. The adherent appendage was divided with relief of the constriction.

Convalescence was uneventful with complete relief of symptoms. On the eighth postoperative day a barium enema was reported as showing no evidence of abnormality in the colon.

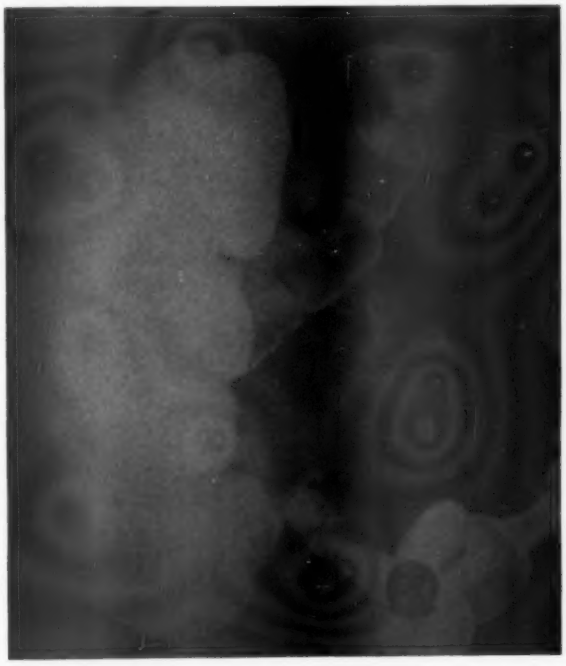

Fig. 1.—Barium enema demonstrating constriction of distal transverse colon.

Case 3.—(Y-4874) H. Q., a 69-year-old white woman, was admitted to the hospital on May 4, 1953, complaining of cramping, left lower quadrant abdominal pain, and obstipation of three days' duration. She had noted progressive constipation with alternate diarrhea for the previous year and anorexia with a 55-pound weight loss in the six months preceding admission. Abdominal distention and nausea were associated with the abdominal pain. Inquiry into the past history revealed an illness at the age of 33 which the patient described as a left ovarian abscess.

Physical examination revealed an emaciated elderly woman who appeared chronically ill. The abdomen was slightly distended, and a mass was visible just inferior and to the right of the umbilicus, which appeared to be a loop of dilated bowel. There was generalized abdominal tenderness, and bowel sounds were hyperactive.

Laboratory examination revealed a hypochromic anemia. Proctoscopy was negative to 17 cm. Three roentgenographic examinations were performed with barium enemas. Two of the examinations were considered unsatisfactory, but all revealed evidence of a filling

defect with narrowing of the transverse colon and partial obstruction to the flow of barium. On May 11, 1953, the third and most satisfactory barium enema was reported as showing a polypoid mass in the mid-transverse colon, probably carcinoma (Figs. 4 and 5).

Surgical exploration on May 14, 1953, revealed obstruction of the mid-transverse colon by a thick, circular, fibrous band which completely encircled the right colon with compression

Fig 2.—Barium enema demonstrating constriction and filling defect of mid-transverse colon.

Fig. 3.—Air contrast spot film of constricted area demonstrated in Fig. 2 suggesting sessile intraluminal lesion with possible ulcer crater.

Fig. 4.—Barium enema demonstrating filling defect with narrowing of transverse colon, probably polypoid carcinoma.

Fig. 5.—Subsequent barium enema examination demonstrating partial obstruction at site of constriction shown in Fig. 4.

of the mid-transverse colon. The ascending colon was short, and the cecum lay high in the right upper quadrant and was abnormally mobile. The fibrous ring was freed and slipped off the right colon intact with complete relief of the obstruction (Fig. 6). The ring was composed of thick, avascular, fibrous tissue with a diameter of approximately 4 cm. (Fig. 7). It was attached to bowel and mesentery only by a few filmy adhesions. Appendectomy and a cholecystectomy for cholelithiasis were performed.

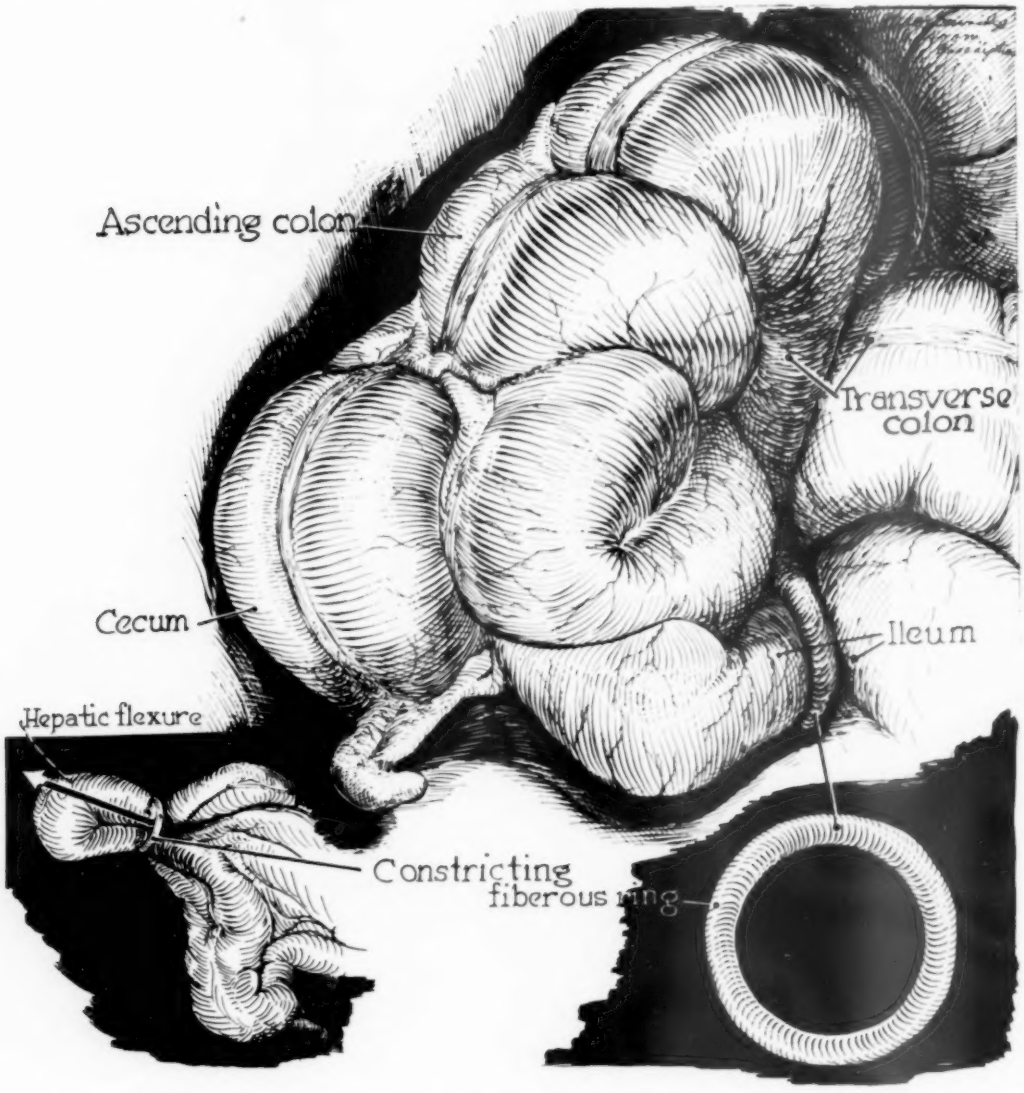

Fig. 6.—Illustration of obstruction of mid-transverse colon by complete encirclement of distal ileum and right colon by fibrous ring; inset lower right. Left lower inset, illustration demonstrating relief of obstruction by reducing the right colon through the intact ring.

The postoperative course was uneventful, and the patient was discharged on May 22, 1953. There has been no recurrence of the preoperative symptoms.

DISCUSSION

There are several unusual causes of deformities of the colon which simulate carcinoma. Diaphragmatic hernias can produce colonic obstruction which is

difficult to distinguish from that due to malignant lesions. Congenital hernias, particularly those occurring through a persistent pleuroperitoneal canal, may produce radiologic distortion of the transverse colon.[37] Lewisohn[25] reported a case of incomplete obstruction of the colon for which a colostomy was performed before the presence of the transverse colon in a traumatic hernia of the diaphragm was discovered at a second operation.

Fig. 7.—Photograph of circular fibrous ring illustrated in Fig. 6. The projection from the upper aspect of the ring represents attached adipose tissue.

Colp[8] collected 167 cases of spasm of the large bowel producing obstruction and reported an additional five cases. Many of these lesions simulated carcinoma, and exploration was carried out in one of his cases with that diagnosis. Spasm is generally encountered in the left half of the colon and, in elderly patients, may strongly suggest carcinoma. The correct diagnosis can usually be made, however, with a barium enema carefully performed, or with repeated enemas.

Residua of previous inflammatory processes in the abdomen occasionally produce obstruction of the colon and symptoms suggestive of carcinoma, the

syndrome of the "fixed omentum" being an outstanding example.[1, 13, 27] Melchior[30] reported an instance of colon obstruction due to infarction of the omentum with spasm of the large intestine.

Retroperitoneal or intra-abdominal masses frequently produce large bowel symptoms and distorted radiographic profiles. This is particularly true when the colon is adherent to, or makes up a part of, the tumor, as in pseudocysts of the pancreas. These lesions seldom produce localized areas of colon involvement, however, and are readily diagnosed with adequate roentgenographic examination.[4]

Abnormalities of large intestinal function and of radiologic appearance due to congenital defects have been recognized for many years.[22] Defects in position and improper fixation are frequently encountered on roentgenographic examination of the large intestine. Fourteen cases of retroposition of the colon have been described. These are characterized roentgenographically by extrinsic distortion.[40] Congenital bands causing obstruction of the colon have been reported and numerous symptoms ascribed to their presence.[28] Meckel[29] and Treitz,[39] in their early work on the embryology of the intestinal tract, described such bands, and later, right-sided congenital bands were indicted as simulating chronic appendicitis. Binnie[5] was the first American author to describe these congenital veils and bands involving the right colon, and later Lane[24] and Jackson[20] described in detail the condition which now bears their names. Two of the four patients reported by Harvey[17] had filling defects resembling carcinoma demonstrated on roentgenographic examination.

In each of the three cases of large bowel obstruction mimicking carcinoma which we have described, the obstruction was caused by a benign extrinsic lesion. The manifestations of weight loss, change in bowel habit, cramping abdominal pain, and rectal bleeding, so typical of neoplasia of the colon, were the essential clinical features of these cases. There were no indications of the extrinsic nature of the constriction and nothing to suggest other etiological factors. Repeated roentgenograms in each case demonstrated constant defects and partial obstruction of the large bowel.

Cases 1 (J. C.) and 2 (C. P. H.) represent extrinsic colon deformities produced by adherence of appendices epiploicae (Fig. 8). Only two similar cases have been reported.[2, 19] Cruveilhier[9] was the first to suggest that the appendices epiploicae could produce intestinal obstruction. Beattie[3] in 1950 collected sixty-five cases of disease of the appendices epiploicae and reported two additional cases. One additional case has been added since his report.[21] Of these sixty-eight cases, intestinal obstruction has been a feature in twelve instances, eight involving the small intestine,[23, 32, 33, 36, 38] and four the colon.[2, 16, 19, 31] Of the latter, one was due to intussusception of an epiploic appendix[16] and one to an inflammatory mass secondary to torsion of an epiploic appendix.[31] The frequent involvement of appendices in pathologic processes[14] makes it surprising that more cases of obstruction have not occurred.

The adherence of the appendices epiploicae is due to inflammatory change within the appendage. The pathologic process is secondary to vascular occlusion

and infarction, with or without torsion.[35, 41] The presence of lymphatic and blood vessels contiguous with the bowel predisposes to inflammatory change.[12] This process usually progresses to the formation of a corpora aliena adiposae, the formation of inflammatory abscesses or masses, or resolution.[15] During the acute inflammatory phase, adherence to adjacent viscera may occur and, as healing takes place, constriction of the bowel may result. Conversely, adjacent inflammatory processes may cause attachment to uninvolved appendices epiploicae. The anatomic structure of the appendages predisposes to attachment to adjacent viscera, particularly when the appendices are exceptionally long.[26] Involvement of the transverse colon in the two cases we have reported is due probably to the anatomic distribution of the appendices epiploicae along this portion of the colon. When this portion of the colon is suspended, the appendices epiploicae attached to the anterior taenia become dependent.[7] In spite of its rarity, this condition should be kept in mind in any instance of unexplained constriction of the colon.

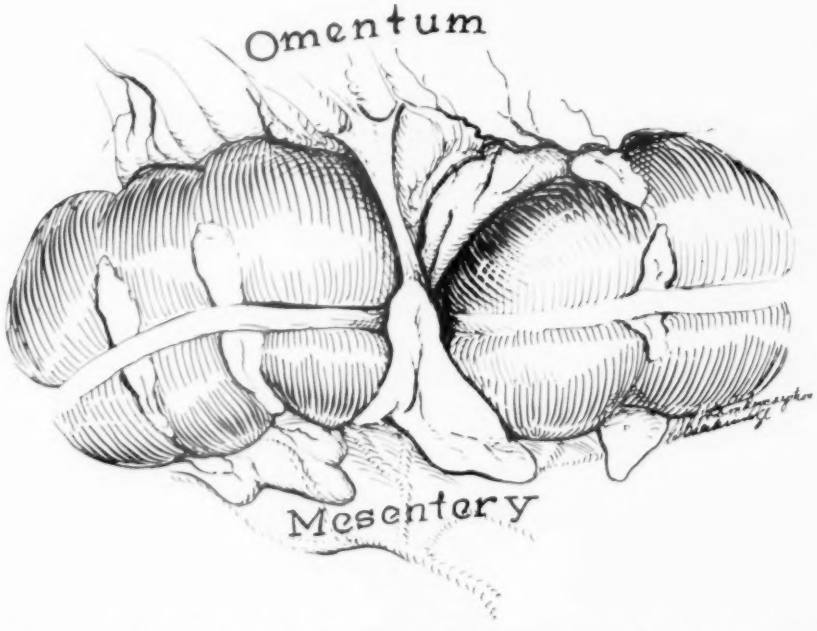

Fig. 8.—Illustration of constriction with partial obstruction of the transverse colon by adherence of an epiploic appendix across the antimesenteric border.

The third case (H. Q.) is an interesting and unusual example of the bizarre conditions that can be produced by intra-abdominal adhesions. That a completely circular and unattached band would encircle all of the right colon and distal ileum is difficult to explain. No other adhesions were present within the abdomen, and its origin was not apparent. The right colon was mobile and unattached, allowing complete encirclement by the "doughnutlike" ring, and facilitated its removal by simply reducing all the right colon through the ring. There have been numerous reports of distortion of the colon by congenital bands and by malposition,[6, 10, 11, 42] but no description of a completely circular band was

found. The possibility exists that this band was secondary to the previous pelvic inflammatory disease but, without the congenitally mobile colon, it could not have assumed its interesting circular pattern.

SUMMARY

Extrinsic lesions may produce constriction of the colon with symptoms and roentgenographic characteristics suggesting carcinoma. The more common causes are usually readily explained. Infrequently diaphragmatic hernia, localized colon spasm, unsuspected retroperitoneal masses, and congenital defects and bands may produce these confusing extrinsic deformities.

Three cases have been described which were erroneously diagnosed preoperatively as carcinoma of the colon but were found at operation to be benign, extrinsic constrictions. In two of the cases, the constriction was due to appendices epiploicae and in the third case to a circular fibrous ring.

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FACTORS IN NEONATAL RESISTANCE TO ANOXIA

II. Effects of Elevated and Reduced Temperature Upon Survival and Recovery by Neonatal Guinea Pigs*

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INTRODUCTION

STANDARD hospital treatment of babies asphyxiated at birth includes the use of warmed bassinets or incubators to maintain normal body temperature. Since the oxygen requirements of living cells vary with temperature, the rationale for this practice has been questioned, and preliminary experiments testing the effects of hypothermia have been reported (Miller, 1949a, 1949b). More recently an extensive series of experiments has been performed on neonatal and adult animals to test the possibility that warming may shorten life during asphyxia and lessen chances of complete recovery, and that cooling may be a lifesaving measure. Results of these experiments have been reported in part in abstract form (Miller, Miller, and Farrar, 1951) and by means of a Kodachrome moving picture (Miller and Miller, 1951). The present article concerns the effects of elevated and of reduced temperatures on neonatal animals only. A companion report will be issued later in which the results upon adult animals will be described.

MATERIAL AND METHODS

Of the common laboratory animals the guinea pig has placental relations most nearly resembling those of man. Likewise, it is the only one born in a more, rather than less, mature stage of development than is man. For these reasons and because histologic studies have already been made demonstrating the effects of anoxia upon the guinea pig central nervous system (Windle, Becker, and Weil, 1944), this animal was selected for study.

Since the data of Glass, Snyder, and Webster (1944) and our own early experiments indicated a greater variability in animals immediately after birth than during the latter half of the first postnatal day, animals were used for experiment in almost all cases between twelve and twenty-four hours after birth.

Asphyxia was produced by exposure to a stream of 95 per cent N_2 + 5 per cent CO_2 flowing through a bell jar. A mixture of the two gases was used in order to prevent CO_2 depletion and thereby to simulate more closely naturally

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occurring asphyxia in which CO_2 accumulates in the body. A 5 per cent concentration was used, since Snyder and Rosenfeld (1937) found that less than 5 per cent CO_2 did not adequately stimulate the respiratory reflexes of fetuses.

Cooling was produced in early experiments by wetting with 95 per cent ethanol and evaporation in a stream of air. In all later experiments, immersion to the neck in ice water was used, since cooling by this method was more rapid. Warming was by exposure to radiant heat.

Temperatures were taken with a U.M.A. skin thermocouple modified so that it could be inserted 2 cm. into the colon. The instrument was calibrated with a United States standard thermometer, and the galvanometer was balanced with ambient temperature before each reading. Readings were taken before and after exposure to gas, and the mean was recorded as the temperature.

All visible reactions were timed with a stop watch. Records were kept of fall-over time, times of all gasps in the gas, and time of removal. In animals which succumbed, the last barely visible gasp was recorded as the time of death (T.O.D.). All animals which died during the experiment were autopsied. For animals that recovered, records also included time (in seconds after removal from gas) and temperature at which each of the following appeared: first breath, first attempted righting reflex, completion of righting, and first crawling. The first breath and righting reflex were selected because they are completely spontaneous and show the least variability. Crawling time, although variable, indicates complete or nearly complete recovery, including the return of volition as well as ability to progress by movement of all four legs.

The following types of experiments were performed:

1. *Survival.*—In these, the times of death at various colonic temperatures were determined for the entire range from lethal heat to lethal cold.

2. *Cooling During Asphyxiation.*—To test the effectiveness of cooling during asphyxiation, the animals were dropped into ice water inside the bell jar after they had lost equilibrium from asphyxiation.

3. *Recovery.*—Using animals at different temperatures, the length of exposure to asphyxia was adjusted so that one animal of each littermate pair died. Stages in recovery of the surviving littermate were timed and recorded.

4. *Rewarming.*—Since reports of German concentration camp experiments on human beings indicate that rapid rewarming in a 45° C. bath is the best treatment for severe hypothermia (Alexander, 1945), a series of experiments was performed to test the effectiveness of rewarming cooled asphyxiated animals.

For lack of means of treating the experimental and control animals in identical fashion, no manipulative resuscitative measures were attempted in any experiments. Therefore, on the one hand, when recovery took place it was entirely spontaneous, and on the other hand, many of the animals which died undoubtedly could have been resuscitated with proper procedures. Experiments in which resuscitation is used are planned for later investigations.

RESULTS

1. *Survival Experiments.*—The first phase of the investigation was to test the effects of temperature upon survival over the entire range from lethal heat to lethal cold. Seventy-five litters with a total of 205 animals were used in this series. Of these, twenty-five died from temperature extremes before experimentation, five above 43° C. and twenty below 19° C. As may be seen in Table I, at temperatures above 44° C. and below 12° C., approximately one-half the animals died before experimentation. Between 12° C. and 16° C. more than one-third succumbed before exposure to asphyxia.

TABLE I. EFFECTS OF TEMPERATURE ON LENGTH OF ASPHYXIAL SURVIVAL OF NEWBORN GUINEA PIGS

TEMPERATURE °C.	DEATHS BEFORE EXPERIMENT		DEATHS FROM ASPHYXIA		
	NO.	% OF TOTAL	NO.	MEAN SECONDS T.O.D.	STANDARD ERROR OF MEAN
44-46	3	50.0	3	90.7	± 4.7
40-44	2	1.1	16	138.1	± 9.8
36-40	-	-	26	187.2	± 7.0
32-36	-	-	15	229.3	±13.9
28-32	-	-	18	291.2	±10.3
24-28	-	-	15	307.0	±11.9
20-24	-	-	18	347.1	±13.8
16-20	2	5.0	38	358.0	±10.9
12-16	15	36.6	27	416.5	±18.4
10-12	3	42.9	4	486.5	±31.4
Total	25		180		

205 animals with colonic temperatures from 45.2° C. to 10.2° C. Time of death in seconds (T.O.D.) of 180 exposed to 95 per cent N_2 + 5 per cent CO_2. Above 43° C. and below 19° C., twenty-five died before experimentation from extremes of temperature.

The remaining 180 were exposed to a mixture of 95 per cent N_2 + 5 per cent CO_2. The shortest survival was eighty-one seconds at 44.2° C., the longest were 614 and 617 seconds at 12.4° C. and 14.0° C., respectively. Mean times of death for the data grouped in 4° temperature classes show an increase in survival time of from 10.9 to 61.9 seconds per 4° decrease in temperature. As indicated by the standard errors, these differences between means of adjacent classes are statistically significant in every case but two. All the differences in means 8° or more apart are significant.

In order to compare survival times of littermates asphyxiated at different temperatures, five typical experiments are shown in Fig. 1. Time of death is plotted against temperature for each animal. A vertical line extending above and below each point indicates the temperature change of the animal during the experiment. The graph shows that some litters are more susceptible to asphyxia at all temperatures than are others. For this reason, summarizing the results of many litters tends to indicate greater variability than is actually the case.

The times of death plotted against temperature for all 205 animals are shown in Fig. 2. On the graph is shown the regression line calculated by the method of least squares for the temperature range in which no deaths oc-

curred before experiment (111 animals).* This shows a linear increase in survival of approximately 50 per cent per 10° C. decrease in temperature with a coefficient of correlation of −0.83. Inclusion of all 180 animals asphyxiated in the experiments resulted in a slight decrease in the coefficient of correlation (−0.81) and a slight decrease in the slope of the line. The occurrence of deaths in the two temperature extremes indicates that complications enter the picture at very high and very low temperatures. It appears likely that if the secondary effects of deep hypothermia (increased blood viscosity with attendant overloading of the heart, interference with respiratory movements, and so forth) can be separated from the primary effects upon cellular metabolism, a sigmoid curve would result.

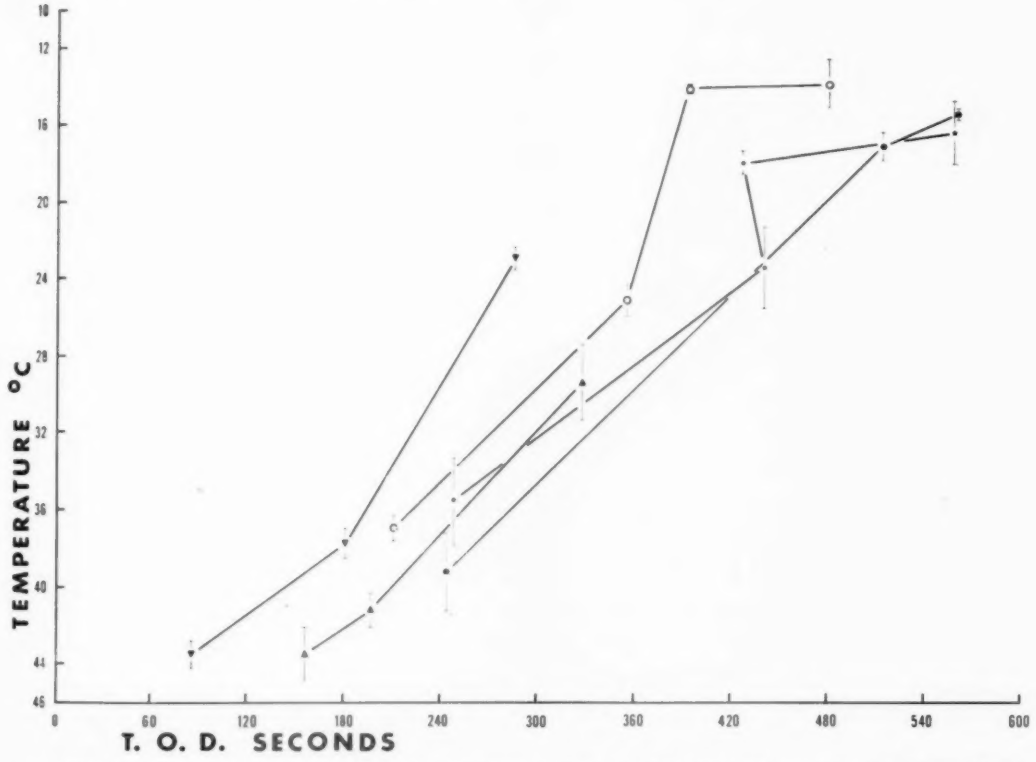

Fig. 1.—Time of death (seconds) and temperature in five typical experiments with three or four animals in each litter. Littermates, indicated by the same symbol, are connected by heavy lines. Fine vertical lines show temperature change for each animal during the experiment.

Morbidity due to cold was obvious in nearly all animals below 19° C. at the beginning of the experiment. Stiffness of the legs, inability to maintain equilibrium, and difficulty in breathing were prominent symptoms. It is of great importance, however, not to overlook the fact that certain animals, which were more resistant to the effects of cold than the average, were greatly benefited by temperatures below 20° C. When factors influencing cold tolerance have been more thoroughly investigated, still lower temperatures may prove to be even more effective in protecting against the effects of asphyxia.

*We wish to thank Mr. Ralph Partington of the Mathematics Department of Emory University for assistance with calculations and curve fitting.

The possible influence of size on asphyxial survival was tested. Using the regression line as a standard, the weights of animals in the 20° C. to 43.5° C. range which survived longer than expected were compared with the weights of those which lived shorter than expected. The mean weights of these two groups were, respectively, 82.5 grams ± 2.3 (standard error of mean) and 91.6 grams ± 2.4 (standard error of mean). This difference is significant at the 1 per cent level. If the regression line were projected to cover the entire temperature range, the mean weights would be 80.8 grams ± 1.9 for those living longer and 88.3 grams ± 1.8 for those living shorter than expected, again a statistically significant difference. However, since the validity of the line above 44° C. and below 20° C. is questioned, no great reliance is placed on these latter figures.

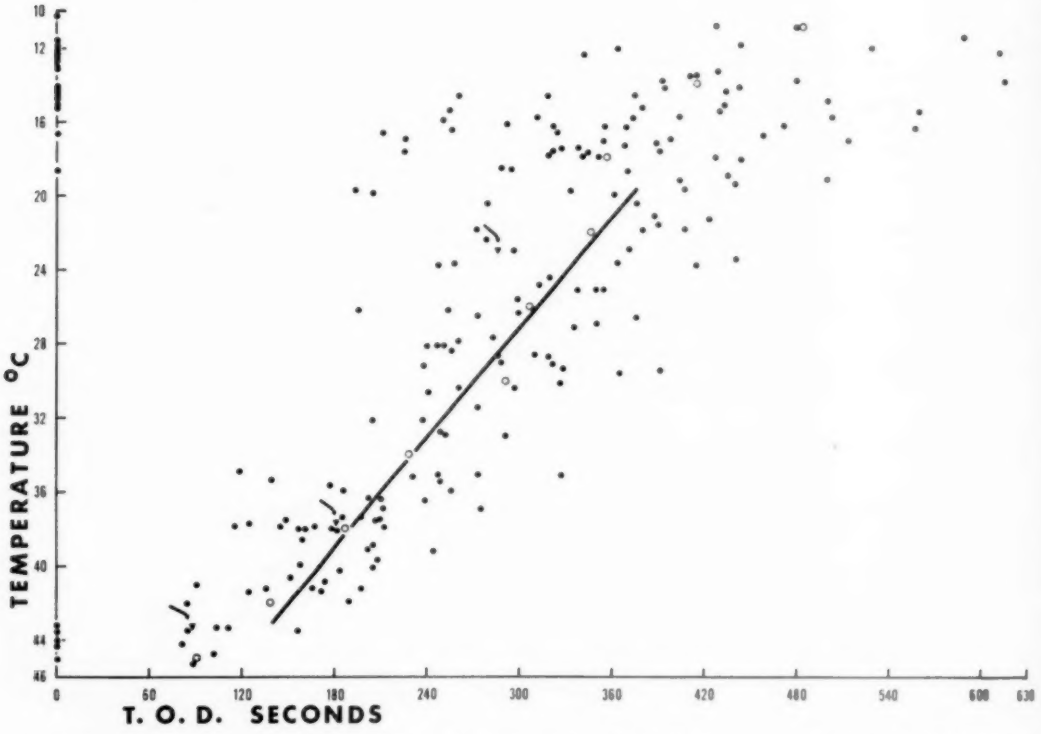

Fig. 2.—Time of death (seconds) and temperature of 205 neonatal guinea pigs asphyxiated with 95 per cent N_2 + 5 per cent CO_2. Dots represent individual animals, stars locate means of 4° classes (Table I). Triangles indicated by arrows represent littermates in moving picture (Miller and Miller, 1951)—one warmed, one control, and one cooled. Regression line calculated for animals between 20° and 43.5°, the range in which no deaths occurred from temperature before asphyxiation. Dots on ordinate represent deaths from heat or cold before asphyxiation.

These results are consistent with the impression that very large fetuses are sometimes stillborn, and are often delivered with difficulty, and therefore may not be as resistant to subsequent asphyxiation as smaller animals. Because of these findings in all subsequent experiments, animals were selected so that the mean weights of the experimental and control animals were kept as close as possible.

Sex had no influence upon resistance to anoxia. Regression lines for each sex were almost identical with each other and with the combined line shown

in Fig. 1. Coefficients of correlation calculated for the range of 43.5° C. to 20° C. were −0.83 for males and −0.84 for females, showing likewise that there was no difference in variability of the sexes in this regard.

2. *Cooling During Asphyxiation.*—To test the effectiveness of cooling after loss of equilibrium from asphyxia, seven litters were used with one control per litter and a total of ten experimental animals (Table II). Controls were asphyxiated at normal temperature. Littermates were placed on wire inside the gas chamber. By manipulation through the top of the chamber, the wire was tilted and the animal dropped into ice water to the neck as soon as it lost equilibrium.

TABLE II. EFFECTS OF COOLING DURING ASPHYXIA ON NEONATAL GUINEA PIGS

	CONTROL			COOLED AFTER FALL-OVER		
LITTER NO.	TEMPERATURE DROP	T.O.D. AFTER FALL-OVER	%	TEMPERATURE DROP	T.O.D. AFTER FALL-OVER	%
1	2.1°	159	100	11.3°	191	120.1
				11.4°	183	115.1
2	1.0°	181	100	10.6°	221	122.1
3	2.1°	224	100	10.3°	224	100.0
4	1.7°	174	100	8.9°	170	97.7
5	1.8°	209	100	13.7°	236	112.9
				14.7°	257	120.1
6	2.0°	187	100	11.7°	203	108.6
				12.4°	243	129.9
7	1.9°	175	100	14.3°	215	122.9
Mean	1.8°		100	11.9°		114.9 ± 2.9
Range	(1.0°-2.1°)			(8.9°-14.7°)		(97.7-129.9)

Time of death (T.O.D. in seconds after fall-over) of seven litters (ten experimental, seven control animals) with cooling started after fall-over time. Asphyxiation produced by exposure to 95 per cent N_2 + 5 per cent CO_2.

Temperatures were recorded at the beginning and end of each experiment and the difference tabulated as the temperature drop. Time from fall-over to last gasp was recorded as T.O.D. Littermate comparisons were calculated as percentages of control. The mean temperature drop of controls was 1.8° C. and that of the cooled animals was 11.9° C., a difference of approximately 10° C. The mean survival time, in percentage of the control, was 114.9 per cent. This is statistically significant at the 1 per cent level, since it is five times the standard error of ±2.9. It should be noted that the only animal which cooled less than ten degrees was also the only one which lived a shorter time than its littermate.

3. *Recovery Experiments.*—When animals were tested in pairs, it was found that cooler animals recovered from exposures which were lethal to warmer littermates.

In preliminary experiments, eight litters (twenty-three animals) 3 to 28 hours old were used (Table III). Temperatures were recorded for each animal but not tabulated, since attempts to calibrate the thermocouple in use at that time showed it to be inaccurate. All nine animals with elevated temperatures died, as also did the four at normal temperature. All ten cooled animals survived exposures considerably longer than necessary to kill their uncooled littermates, and nine recovered completely. When littermates were compared, in every case the warmest animal died first, the animal at normal

temperature died next, and the cooled animal was alive when removed from the gas thirteen to ninety seconds later. The one cooled animal which failed to recover was unusually large (142 grams), only 3 hours old, and subjected to the longer of the two periods of asphyxia used. Very large animals frequently have difficult deliveries and sometimes show evidence of birth injury. Both of its littermates (also large) had shorter than average survival times.

TABLE III. PRELIMINARY RECOVERY EXPERIMENTS

	WARMED		UNTREATED (AT NORMAL TEMPERATURE)		COOLED			
					REMOVED AT 255 SECONDS		REMOVED AT 270 SECONDS	
	NO.	T.O.D. (SECONDS)	NO.	T.O.D. (SECONDS)	NO.	T.O.D. (SECONDS)	NO.	T.O.D. (SECONDS)
Recovered	0	—	0	—	4	—	5	—
Died	9	172.1 (120-239)	4	211 (165-257)	0	—	1*	322

Eight litters (twenty-three animals) of neonatal guinea pigs exposed to 95 per cent N_2 + 5 per cent CO_2. In four litters the exposure was 255 seconds, in four litters 270 seconds. In four litters one animal was untreated and at least one animal was warmed and one cooled.

*Note text discussion of this exceptional animal.

Using a new calibrated thermocouple, ten litters of four animals were tested. In five litters the temperatures of the animals were adjusted to approximately 40° C., 30° C., 25° C., and 20° C. In the other five they were 35° C., 25° C., 20° C., and 15° C. In each case the cooler animals were exposed fifteen seconds longer than the time that was necessary to kill the warmest littermate. The upper half of Table V shows that down to 20° C. 100 per cent of the cooler animals recovered completely from exposures lethal to the warmest littermate. At 20° C., however, although all the animals lived longer than their controls (see column 1 under "Deaths"), spontaneous recoveries did not always occur. None of the 15° C. animals recovered. It will be noted that among the animals that recovered, the coolest required the longest time to exhibit the righting reflex. The same was true for each of the four stages of recovery which were timed (Table IV).

TABLE IV. EFFECTS OF TEMPERATURE ON RECOVERY TIME

TEMPERATURE °C.	NO. OF GASPS IN GAS	DEATHS		REMOVAL (SECONDS)	RECOVERY				
		NO.	T.O.D.		NO.	1ST BR.	ATT.R.R.	COMPL.	CRAWL
40.1	32.4	5	212.0	227.8	0	–	–	–	–
28.4	10.6	0	–	227.8	5	129.8	244.8	258.8	523.6
24.7	8.2	0	–	227.8	5	148.6	520.0	538.8	861.0
19.8	6.0	0	–	227.8	5	247.6	758.0	872.8	1334.6

Five litters of four animals, each exposed at a different temperature. All values are means of five animals. T.O.D. = time of death in seconds. Recovery times are seconds after removal from gas (95 per cent N_2 + 5 per cent CO_2). 1st br. = first breath, Att.r.r. = first attempted righting reaction, Compl. = completion of righting.

These results made it necessary to determine whether this delay in recovery was caused by a deleterious effect of low temperature, or whether it was merely the result of the reduction in life processes at lower temperatures and of the greater time required by the coolest animals to return to normal temperatures. Littermate pairs were tested after adjusting their temperatures so

that one member of the pair was approximately 10° cooler than the other. The lower half of Table V shows that 30° animals recovered from exposures which were lethal to 40° animals, 25° animals recovered from exposures lethal to 35° animals, and that approximately one-half the 20° animals recovered from exposures which were lethal to 30° animals. In addition, the nine 20° animals which failed to recover still lived an average of 14.7 per cent longer than their 30° littermates. As found in the survival experiments, under the conditions of these experiments, temperatures below 20° C. may be hazardous. None of the 15° animals recovered from exposures lethal to 25° littermates, and the cooler animals actually lived only 94.2 per cent as long as the warmer.

TABLE V. RECOVERY OF COOLER LITTERMATES AFTER DEATH OF WARMER CONTROL

	DEATHS			RECOVERIES					
				RIGHTING REFLEX—SECONDS AFTER REMOVAL					
EXPERIMENT	T.O.D. (SECONDS)	APPROXIMATE TEMPERATURE	EXPOSURE (SECONDS)	40°	35°	30°	25°	20°	15°
5 litters (20 animals)	212.0	40°	227.8	All died	---	244.8 (100%)	520.0 (100%)	758.0 (100%)	--- All
5 litters (20 animals)	280.8 304.0 330.0	35° 20° 15°	295.8	---	All died	---	879.4 (100%)	1230.5 (40%)*	died†
5 litters (10 animals)	215.6	35°	232.6	---	All died	---	347.6 (100%)	---	---
10 litters (30 animals)	323.4 337.7	30° 20°	337.7	---	---	All died	---	1078.1 (47.1%)*	---
10 litters (20 animals)	330.1 310.9	25° 15°	345.1	---	---	---	All died	---	All died*

Thirty-five litters (100 animals) with temperatures adjusted as indicated and exposed to 95 per cent N_2 + 5 per cent CO_2 until one member of the litter died. Fifteen seconds later all animals were removed from the chamber to permit spontaneous recovery.

*Mean survival time of animals which died was greater than that of the warmer littermates.

†Mean survival time of this group was 94.2 per cent of that of 25° littermates.

It is concluded from these experiments that cooling to approximately 20° will not only prolong asphyxial survival but will permit complete recovery from bouts of asphyxia which are lethal to warmer littermates.

Table VI shows that although there was a progressive increase in temperature during recovery, there was no specific temperature, within the range of the experiments, at which a given reflex will reappear. First breaths occurred at mean temperatures of 26.7° C., 24.1° C., and 21.2° C. Similarly, the righting and crawling reflexes reappeared at lower temperatures in the colder series than in the warmer. Moreover, the animals cooled to approximately 20° were able to crawl at a mean temperature of 25.8° C., which was 0.9° C. below that at which the 30° group took their first breath, and one of the 20° group crawled at 23.6° C. It therefore appears reasonable to interpret the increase in temperature as one reads down Table VI to be merely a reflection of the increased length of time needed to reach the more advanced stages of recovery.

4. *Rapid Rewarming.*—Since it has been reported that rapid rewarming is beneficial to human beings suffering from acute hypothermia (Alexander, 1945), experiments were performed to test the effect of this treatment upon the recovery of animals which had been cooled and asphyxiated (Table VII). Twenty experiments were performed using littermate pairs cooled to 20° C.

before asphyxiation. The exposures were adjusted to be lethal for about one-half the animals. In eight experiments both animals recovered, in five both died. In four the rewarmed animal recovered and its littermate died, in three the rewarmed animal died and its control recovered. Since a total of twelve rewarmed animals and eleven untreated littermates recovered, it is concluded that rewarming does not increase the chances of recovery of cooled, asphyxiated animals.

TABLE VI. RELATIONSHIP BETWEEN TEMPERATURE AND STAGES OF RECOVERY

STAGE OF RECOVERY		30° SERIES	25° SERIES	20° SERIES
1st Br.	Mean	26.7°	24.1°	21.4°
	Range	(25.6°-27.4°)	(23.5°-25.2°)	(20.5°-22.8°)
Att. r.r.	Mean	26.9°	25.2°	23.5°
	Range	(25.6°-27.5°)	(24.1°-26.7°	(21.6°-25.3°)
Compl. r.r.	Mean	27.6°	25.2°	24.2°
	Range	(25.6°-29.9°)	(24.1°-26.7°)	(21.8°-26.5°)
Crawl	Mean	29.1°	27.4°	25.8°
	Range	(27.7°-30.8°)	(25.6°-28.7°)	(23.6°-29.0°)

Temperatures at each stage of recovery for animals whose righting times are given in Table V. Temperatures of animals in 30° series continued to drop during and immediately after experiment, resulting in low temperatures.

TABLE VII. EFFECTS OF RAPID REWARMING ON RECOVERY OF COOLED ASPHYXIATED NEONATAL GUINEA PIGS

		BOTH RECOVERED			WARMED RECOVERED			CONTROL RECOVERED		
			RIGHTING REFLEX			RIGHTING REFLEX			RIGHTING REFLEX	
	NO.	NO.	TIME†	TEMPERATURE	NO.	TIME†	TEMPERATURE	NO.	TIME†	TEMPERATURE
Control	20*	8	817	24.3°	4	Died	Died	3	580.3	25.7°
Warmed	20*	8	449	31.3°	4	421.5	31.6°	3	Died	Died

Twenty littermate pairs of 1-day-old or younger guinea pigs cooled to approximately 20° and asphyxiated until very weak. Controls allowed to recover at room temperature. Experimental animals placed in a water bath at 45° until ready to breathe.

*In five experiments neither animal recovered.

†Time (in seconds after removal from bell jar) of first attempt to right.

On the other hand, Table VII shows that rewarming brings about a more rapid recovery in animals which are able to survive. Using the first righting reflex as a point of reference, the rewarmed animals recovered in 55 per cent of the time required by their littermates (calculated from column 4) even though the temperature differential was only 7° C.

Autopsy Findings.—All animals dying from the experiments were autopsied. Congestion of the lungs with hemorrhagic areas of varying sizes was a constant finding. Subcapsular hemorrhages of the adrenals, engorgement of the vessels of the digestive tract, hyperemia, and hemorrhages of the upper pole of the testis or (in females) engorged uterine vessels were usually noticeable also.

The hearts were carefully observed for evidence of damage, with hyperemia a common finding and occasional instances of hemorrhage of the coronary arteries, particularly the anterior descending branch of the left coronary. When autopsies were performed within a few minutes of death, the atrial beat and often also the ventricular beat could be started again by mere re-

moval of the pericardium and exposure to the air. It was rare, however, that coordinated beating returned, and still more unusual for effective pumping action to reappear in these hearts.

Because careful studies of the effects of severe asphyxia upon the central nervous system of neonatal guinea pigs have already been made (Windle, Becker, and Weil, 1944), no intracranial examinations were made in these experiments.

Hyperthermic animals showed very rapid beat of atria and pulmonary veins. Massive lung hemorrhages were consistent in this group. Another striking observation in these animals was the appearance of rigor mortis almost immediately after the last gasp.

Animals in the lowest temperature ranges, which survived a much longer period of asphyxia, also showed numerous hemorrhages of the lungs. The hearts of many of these animals were enlarged and hyperemic.

General Observations.—There was a regular sequence of events during asphyxiation and recovery. Animals at normal body temperature first showed increasing hyperpnea and hyperactivity. After about eighteen seconds (range twelve to twenty-four), they lost equilibrium and exhibited running movements and convulsive seizures for twenty to thirty seconds. This was usually followed by a period of ten to twenty seconds of apnea after which they gasped at a constant rate of about once every six to ten seconds, varying with the individual animal. As they became moribund, the rate of gasping increased and gasps became shallower. Finally, there was a terminal series of weaker and weaker gasps, one or two seconds apart, involving chiefly the circumoral musculature. Animals removed at the beginning of this series regularly failed to recover spontaneously. In these experiments, the last of this series of gasps was recorded as the time of death (T.O.D.).

One of the most conspicuous characteristics of cooled animals was a slowing of all reflexes. Indications of this were lessened activity, longer interval before loss of equilibrium, and slower gasping rate. Terminal gasps were weaker but usually not much closer together and in some cases below 20°, were twenty to fifty seconds apart.

There was likewise a regular sequence of events during recovery. First the rate of gasping increased. As the animals' condition improved, the depth decreased. After the first breath, there was usually a period during which the animals took occasional gasps between breaths. This was followed by a period of breathing at about one-half the normal rate, and finally, with the increase to normal rate, reflexes began to be elicitable. The earliest reflex to reappear was the corneal reflex, followed by the anal reflex, pinching reflex, righting reflex, and startle reflex. Crawling, which involves the return of volition as well as the movement of all four legs, followed shortly after the startle reflex in lightly asphyxiated animals. In severely asphyxiated animals, however, its appearance was often greatly delayed.

Because of their spontaneous origin, the first breath, beginning of righting reflex (when the animal raises its head off the substrate), completion of righting reflex (when it succeeds in getting up onto all four feet), and crawling time were used for timing stages in recovery.

DISCUSSION

Neonatal death is, perhaps, the greatest problem in obstetrics today. With the advent of antibiotics, vitamins, and general improvement in all medical care, maternal deaths associated with birth are approaching the vanishing point (Pillsbury, 1953). However, even in the best of hospitals, the hazards of birth to the child have not been greatly lessened from those of ten or twenty years ago, and the estimate of 50,000 lives of viable babies wasted each year in this country alone is a conservative one. Autopsy findings incriminate asphyxia as the greatest single cause of neonatal death (Snyder, 1949; Potter, 1952) with percentages varying from about 20 to as high as 68 (Cruickshank, 1930), depending upon the investigator.

The sequelae of asphyxia are well known in experimental animals. For the guinea pig, Windle and Becker (1943) found that animals recovering from experimental asphyxia neonatorum exhibit a range of neurological symptoms from cerebral palsies and epileptiform seizures to somnolence. Less severely asphyxiated animals, which apparently recovered completely from the treatment, had trouble learning a maze which was easy for nonasphyxiated littermates, and forgot their lessons sooner (Becker, 1946; Becker and Donnell, 1952). Histologic studies on these animals disclosed damage in the thalamus, sensory pathways, and, in some cases, widespread reduction in cell number in the cortex (Windle, 1950).

That alterations in the mental and psychic make-up occur in adults as a result of severe asphyxia is well recognized. That asphyxia at birth may produce palsied children, dullards, or social misfits as well as dead babies is not as generally accepted. Some of the evidence tending to confirm this concept is listed later in the article. Schreiber (1938) reported that 70 per cent of a large group of children with brain defects were known to have been asphyxiated at birth. Darke (1944) compared the intelligence quotients of sixteen children without neurological symptoms whose hospital records showed severe asphyxiation at birth with that of their nearest relatives (siblings or parents). He found a decrease in intelligence which was significant at the 1 per cent level.

To obtain data of unquestioned validity on this problem it would be necessary to study pairs of babies with identical ancestry (that is, identical twins), one of whom was asphyxiated at birth, while the other was born without difficulty. One such case was reported by Preston (1945) among 132 problem children in whom asphyxia neonatorum was found in their birth histories. At 10 years of age, the twin with uneventful birth was bright, well adjusted, and well liked. By contrast, his twin brother, who had been born severely asphyxiated, was nervous and irritable, without friends, and in constant social and scholastic difficulties. This controlled although unplanned experiment confirms in man the findings of Windle and Becker on the guinea pig and gives substance to the growing feeling among those in clinical practice (Means, 1948; Snyder, 1949; editorial, *Lancet,* 1950; Little and associates, 1952; and others) that asphyxia in the newborn child is fraught with danger not only to the life of the baby, but also to the intelligence and future social adjustments of the children who recover without patent neurological symptoms.

There appears to be no experimental or rational basis for the use of heat in the treatment of asphyxia. On the other hand, the rationale for the use of hypothermia is based upon the laws of physics and chemistry (Van't Hoff's law) and a large body of experimental evidence which shows that cellular metabolism in invertebrates and vertebrates drops with temperature. Even in the warm-blooded mammals, if the homeostatic mechanisms are blocked by nature (in hibernation), by drugs, or by anoxia, the need for oxygen is reduced by cold.

The approach to the problem reported here was suggested by the findings of Himwich that poikilothermia is an important factor in the resistance of mammalian fetuses to asphyxia (Fazekas, Alexander, and Himwich, 1941; Himwich and associates, 1942). Since the most far-reaching effects of asphyxia neonatorum are those on the central nervous system, the work of Van Harreveld and Tyler (1944) is of importance. They demonstrated that functional and histologic damage to the spinal cord of cats was less after 120 minutes of asphyxiation when cooled 10° C. than after thirty-five minutes in controls at normal temperature. Our experiments show that, in the neonatal guinea pig, cooling, at least to 20° C. in unanesthetized animals, makes possible complete and spontaneous recovery from a period of asphyxia which is two or more times as long as that lethal to uncooled littermates.

It is well known that severe hypothermia causes shivering, ventricular fibrillation, paralysis of the muscles of respiration, and increase in blood viscosity. No attempt was made in these experiments to control or combat these secondary effects of cooling. Undoubtedly, when these complicating effects are controlled, temperature reduction will be found to be even more effective as a protection against the effects of asphyxia in the newborn child. Dogs, which ordinarily die from hypothermia at about 23° C., when given anesthesia and artificial respiration can safely be carried to 20° C. (Bigelow, Lindsay, and Greenwood, 1950) or even lower (16.2° C., Hegnauer, Flynn, and D'Amato, 1951). In experiments to be reported elsewhere it has been found that the combination of narcosis with cooling increases the resistance of guinea pigs to asphyxia over that of cooling alone, and permits temperature reduction to considerably less than 20° C. (Miller and Miller, 1953b, 1954).

The literature reveals many evidences that low temperature does not damage human tissues and is beneficial in asphyxial states. It lessens pain and reduces the need for amputation in frostbite. In this condition, tissue anoxia in the ischemic areas is an important complication (Webster, Woolhouse, and Johnston, 1942). It prevents the development of shock from amputations and has reduced the mortality of these operations in one hospital from 55 per cent to 15 per cent (Crossman, 1951). It is equally effective in treating shock after it has developed (Allen, 1943, 1948, 1950; Laborit, 1953; Laborit and Huguenard, 1953). Because of its value in reducing shock it was standard treatment for crush injuries in England during World War II. Its use for eighty-nine days eliminated the necessity of an amputation in a case of cellulitis of a leg (Safford and Nathanson, 1944). It has prevented death of a finger accidentally severed from the body for four hours and permitted reunion (Crossman, 1951).

A question may be raised with regard to the limits of human tolerance to hypothermia. The best studied and controlled cases have generally been poor risks. Fay (1940) reported over 100 cases of prolonged refrigeration with the aid of sedation of hopeless cancer patients. The longest period of refrigeration reported was eight days with temperature maintained between 88° and 90° F. The lowest temperature from which there was recovery was 75° F. Talbott (1941) reported one cancer patient carried to 74° F. (= 23.3° C.) and another to 75° F. (= 23.9° C.). In the experiments at Dachau upon unanesthetized and more or less starved subjects, death usually occurred between 24.2° C. and 25.7° C.; however, one subject recovered from 25..2° C. (Alexander, 1945). Recently thoracic surgeons have begun to use hypothermia in operations on the heart. To date, the most successful published reports of these have been from the group at Denver (Swan and coworkers, 1953; Zeavin and associates, 1954), who carried fifteen patients to temperatures between 28° C. and 21.5° C. with only one operative death, and it could not be attributed directly to the low temperature.

In the light of the findings that narcotized animals tolerate lower temperatures better than nonnarcotized animals, it is significant that the lowest temperature from which recovery has been recorded was that of an inebriate (Laufman, 1951). This case is of interest because of a known history of eleven hours' exposure out of doors to temperatures which fell to approximately 10° F. and because of the complete clinical record of the case. The estimated body temperature of 16° C. was extrapolated from the temperature recovery curve. The first reading, taken one and one-half hours after admission, was 18° C.

Tolerance to both cold and asphyxia in newborn animals of all species which have been tested is greater than that of the adults (Boyle, 1665; Edwards, 1824; Kabat, 1940; Fazekas, Alexander, and Himwich, 1941; Glass, Snyder, and Webster, 1944; Fairfield, 1948; Adolph, 1948, 1951; and others). The limit of tolerance to hypothermia in newborn human babies is not known. A 3° F. postnatal drop in temperature is normal (Smith, 1951). Almost any obstetrician with wide experience in home deliveries can cite instances in which gasping recommenced spontaneously in apparently stillborn babies who had developed hypothermia, and there are instances of resuscitation of babies from snowdrifts. Unfortunately no accounts of these in which temperatures were taken have come to our attention. Eckstein (1926) reported that of twenty-one premature infants whose admission temperatures ranged from 34° C. to 26° C., fifteen (71 per cent), including the baby at 26° C., had uneventful sojourns in the hospital. Since a 29 per cent mortality among premature infants given the best of care is not uncommon even today, it may be assumed that low temperature was not responsible for the deaths which occurred in this series. Klein (1936) reported the recovery of a 1-month-old infant from unconsciousness produced by a fall, and from 18° C. rectal temperature. In contrast to Klein's interpretation, we submit that the hypothermia, instead of contributing to the injury, may have actually protected the infant from the development of permanent neurological symptoms or of terminal shock.

From animal experiments, the prediction may be made that lethal cold for full-term babies is several degrees lower than that for adults, and for premature infants is lower still.

Whether or not hypothermia can be used successfully to treat asphyxia neonatorum in man remains a question. Its trial has been suggested on more than one occasion (Miller, 1949a, 1949b; Miller, Miller, and Farrar, 1951; Miller and Miller, 1953a). Until it is tried, the answer must remain in the field of conjecture. However, from the experiments reported here and other still unpublished data, successful results can be predicted. Hypothermia is tolerated well by adults even in poor condition—witness the use in the terminal stages of cancer, and in operations on the heart and great vessels where cyanosis and asphyxia are complications. Likewise, premature infants, whose grasp on life is considered very insecure, recover from severe cooling with no ill effects (Eckstein, 1926). Records of recovery from unusually long periods of apnea at birth do not come from the best hospitals where babies are kept in warmed bassinets but are commonly from home deliveries in winter with the baby "cold as ice" when gasping recommenced.

Finally, with the information which is at hand on methods to prevent shivering (Bigelow and associates, 1950; Laborit, 1953; Miller and Miller, 1954), maintain respiration, and control the fibrillation which occurs at very low temperatures (Swan and co-workers, 1953; Zeavin, Virtue, and Swan, 1954), the use of hypothermia as an adjunct to other resuscitative measures should be tested in the human infant.

SUMMARY

1. Three hundred eighty-five neonatal guinea pigs were tested for the effects of variations of colonic temperatures upon resistance to asphyxia in 95 per cent N_2 + 5 per cent CO_2.

2. In survival experiments (205 animals), a linear increase in length of asphyxial survival of approximately 50%/10° decrease in colonic temperature was found between 43.5° C. and 20° C. Temperatures above 43.5° C. caused deaths before experimentation. Below 20° C. results were variable; some animals died from the effects of excessive hypothermia before experimentation, others survived very much longer periods of asphyxia than expected.

3. When cooling was started during asphyxiation, there was a mean temperature drop of approximately 10° greater in the experimental than in littermate control animals. Life expectancy was increased 14.0 per cent by this treatment.

4. Cooled animals recovered completely from exposures lethal to uncooled littermates. Cooling to approximately 20° C. permitted recovery from asphyxia which was lethal to littermates 10° C. or more warmer.

5. Rapid rewarming (in a bath at 45° C.) of cooled, severely asphyxiated animals caused a more rapid recovery of animals which survived, but did not increase the number of survivors.

6. Autopsy findings included congestion of the lungs, subcapsular hemorrhages in the suprarenals, hemorrhages of the testes or uteri, and hyperemia with occasional hemorrhages of the digestive tract and coronary arteries.

CONCLUSIONS

1. Elevation of temperature is deleterious, and reduction to a minimum of 20° C. is beneficial in asphyxia neonatorum in the guinea pig.

2. Similar findings on other animals and information on the neonatal human being suggest that hypothermia, when tried, will prove beneficial for asphyxiated human babies as well.

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EXPERIMENTAL STUDIES OF GALLSTONE FORMATION

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THE cause and mechanism of gallstone formation are incompletely understood. Once formed, there is no known means of redissolving, in situ, the normal biliary constituents of which the stones are composed. Since gallstones are of etiological importance to many of the gall bladder's pathologic conditions, further study of gallstone formation is indicated. A fundamental process of cholesterol biochemistry may be elucidated in such a study, since the more common variety of gallstone is composed of from 75 to 95 per cent cholesterol.[1]

During experiments on muscular dystrophy, Dam and Christensen[2] incidentally observed gallstones to be present in the gall bladder of hamsters fed a "cholesterol-free and very nearly fat-free diet." They reported gallstones to be present in sixteen of eighteen hamsters fed the diet for at least eighty-seven days. Gallstones were found in only one of fourteen animals fed the diet for less than eighty-seven days. Five samples of gallstones were found to contain from 51.0 to 90.5 per cent cholesterol.

These findings suggested that hamsters might be used as an experimental animal in the study of the various problems concerned with gallstone formation. This paper reports preliminary data from experiments which were conducted to evaluate the observations of Dam and Christensen and to gain further insight on the pathogenesis of gallstone formation.

MATERIALS

Syrian hamsters were obtained from a commercial hamster farm. They were of weanling age and weighed 25 grams (±2) when started on the experiment. The animals were maintained in an air-conditioned room under identical conditions. Water and diet were given ad libitum. The number of hamsters in each experiment was equally divided as to sex.

The composition of the test diet was that specified by Dam and Christensen (Table I). The vitamin A and D preparation was the same as that used by Dam and Christensen, and was generously supplied by the A/S Ferrosan Company, Copenhagen. All the vitamin preparations were aqueous solutions in which the vehicle was composed of 0.114 mg. peanut oil, 0.1 Gm. Tween 80, 1 mg. ethyl gallate per milliliter. The vitamin A and D preparation contained 7,000

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I.U. A natural esters and 103 I.U. D_2 per milliliter. The vitamin A preparation contained 7,000 I.U. A natural esters. The vitamin D preparation contained 103 I.U. D_2 per milliliter.

TABLE I. DIET

Casein (vitamin free) (contained not more than 0.01% fat)	20.0 Gm.
Sucrose	74.3 Gm.
U.S.P. XIII salt mixture No. 2	5.0 Gm.
Choline chloride	0.2 Gm.
Vitamin mixture	0.5 Gm.
Total	100.0 Gm.

Each preparation was administered by pipette to each animal daily, five times each week in 0.035 c.c. quantities.

Vitamin Mixture.—This consisted of biotin 0.05 mg., folic acid 0.05 mg., ascorbic acid 5.0 mg., thiamine hydrochloride 5.0 mg., riboflavin 5.0 mg., pyridoxine hydrochloride 5.0 mg., calcium pantothenate 5.0 mg., nicotinic acid 8.0 mg., inositol 15.0 mg., p-aminobenzoic acid 35.0 mg., vitamin K 3.0 mg. + sugar up to 500 mg. Twenty-five milligrams of Antabuse or 20 mg. d-l-α-tocopherol acetate was added to each 100 grams of diet as indicated in the text.

METHODS AND RESULTS

Ninety-two hamsters were fed the fat-free diet. Vitamin A, 1,225 I.U., and 18.0 I.U. of vitamin D_2 were given to each animal weekly, as described in the previous section.

Sixty-two of the animals died within sixty days. Fourteen animals lived eighty-one days or longer. Gallstones were found in six animals: those dying on the thirty-eighth, fifty-first, fifty-fifth, seventy-fifth, eighty-seventh, and one hundred second days of the experiment.

Since the animals were maintained on a nearly fat-free diet, it was postulated that gallstone formation might have occurred as a result of the absence of dietary fat per se or of the deficient absorption or utilization of the supplementarily administered fat-soluble vitamin A or D.* The experiment was then repeated with synchronous experiments in which no vitamin A was given and another in which no vitamin D was given. An attempt to increase the longevity of these animals was made by using d and l α-tocopherol acetate instead of the Antabuse which had been used in the test diet of the previous experiment.

The experiments were as follows:

(a) One hundred hamsters were given the test diet and vitamin A and D preparation as described previously. Eighty-five of the animals died within sixty days. Only three animals lived eighty-one days or longer. Gallstones were found in ten animals: in one of the twenty-seven animals dying between the thirty-first and fortieth days, in seven of thirty-nine animals dying between

*The effect of dietary fat on gallstone formation will be reported on in a subsequent publication.

the forty-first and sixtieth days, and in two of thirteen animals dying between the sixty-first and eightieth days of the experiment. Gallstones were not present in either of two animals sacrificed on the ninety-second day of the experiment. An additional two animals had black flecks in their gall bladders.

(b) One hundred hamsters were given the test diet and 18.0 I.U. of vitamin D_2 per week. Vitamin A was not given. Eighty-five of the animals died within sixty days. Only two animals lived longer than eighty days. Gallstones were found in twenty-six animals: in four of twenty-two animals dying between the thirty-first and fortieth days, in fifteen of thirty-five animals dying between the forty-first and sixtieth days, in six of eleven animals dying between the sixty-first and eightieth days, and in one of two animals sacrificed on the ninety-second day of the experiment. Bluish green flakes were seen in the gall bladder of a few additional animals.

(c) One hundred hamsters were given the test diet and 1,225 I.U. of vitamin A natural esters per week. Vitamin D was not given. Only three hamsters lived longer than sixty days. Gallstones were found in seventeen animals: in one of twenty-seven animals dying during the first thirty days of the experiment, in two of thirty-four dying between the thirty-first and fortieth days, in twelve of thirty-seven dying between the forty-first and sixtieth days, and in two animals sacrificed on the ninety-second day of the experiment.

Fig. 1.—Gallstones within the thin-walled gall bladder (about ×4; reduced ¼).

In an effort to determine if gallstone formation occurred in hamsters subjected to standard laboratory conditions, the following groups of animals were investigated:

(a) Nineteen hamsters fed the standard laboratory diet and biweekly supplement of sunflower seeds for 113 to 116 days.

(b) Nineteen hamsters 8 to 23 months of age. Most of the animals were older than 10 months (obtained from commercial hamster farm, said to have been fed Purina Laboratory Chow and a supplement of green vegetables).

(c) Sixteen female hamsters which had borne litters and were more than 3 months old (obtained from commercial hamster farm, said to have been fed Purina Laboratory Chow and a supplement of green vegetables).

(d) Nine male and nine female castrated hamsters fed the standard laboratory chow without supplement for three months postcastration.

Gallstones were not found in any animals in these groups.

Summary.—From these data, it would seem that the hamsters did not form gallstones when fed a presumably balanced laboratory diet. However, gallstones were formed in animals which were fed a nearly fat-free diet. The incidence of gallstone formation was apparently increased by withholding either vitamin A or vitamin D_2 from the diet. The observed difference in incidence of gallstones formed in the vitamin A-deficient experiment, as compared to the control experiment in which vitamins A and D were given, is three times the standard error of the difference, and therefore is unlikely to have arisen by chance. However, the difference in incidence of gallstone formation in the vitamin D-deficient experiment, as compared to the control experiment, is less than twice the standard error of the difference, and therefore could have happened by chance.

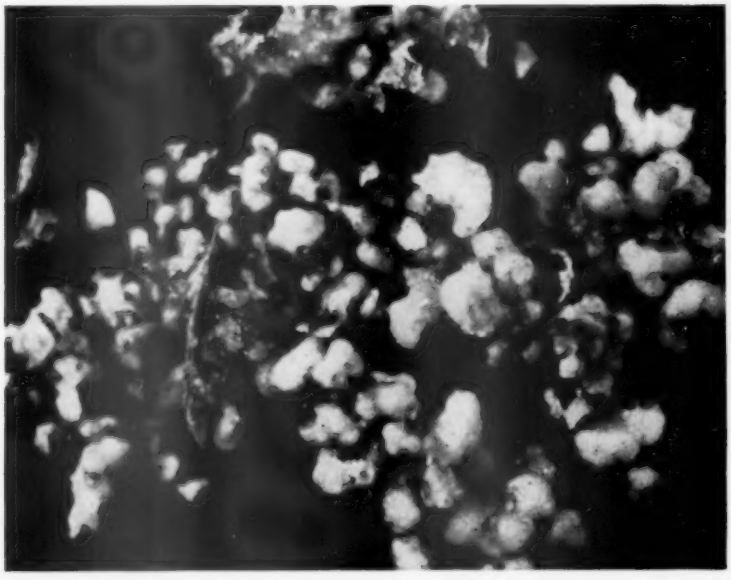

Fig. 2.—Gallstones obtained from the gall bladder pictured in Fig. 1. The aggregation weighed 2.1 mg. and contained 1.5 mg. (71 per cent) of cholesterol (about ×20; reduced ⅕).

MORPHOLOGY OF THE GALLSTONES

The gallstones could be seen lying within the thin-walled gall bladder and, occasionally, within the lumen of the cystic or common bile duct (Fig. 1). A gall bladder commonly contained from one to six or more stones, which varied from 0.5 to 1 mm. in diameter. An occasional gall bladder was filled with innumerable stones of varying sizes and shapes (Fig. 2). The stones were commonly white or pale yellow, moderately firm, round, ovoid, or quite irregular in

outline. Many of the larger stones appeared to be fused aggregates of smaller stones (Fig. 3). The surfaces of the gallstones were smooth, undulated, or bristled with needlelike projections. With magnification, it was seen that the uneven surfaces were formed by the projected, jagged, irregular edges of the aggregated crystalline mass (Figs. 4 and 5).

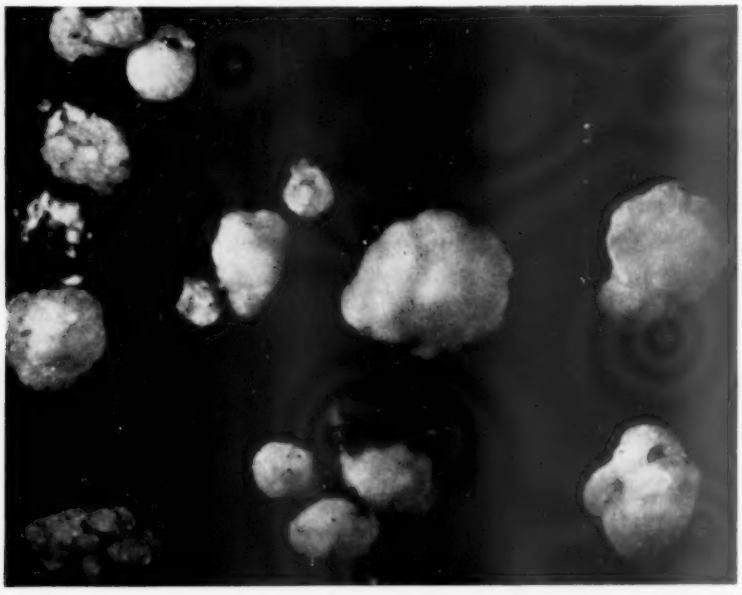

Fig. 3.—Many of the gallstones appear to be fused aggregates of smaller stones. These were obtained from one gall bladder and weighed 2.0 mg. They contained 0.95 mg. (47.5 per cent) cholesterol (about ×20; reduced ⅕).

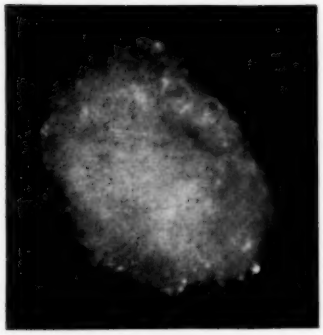

Fig. 4.

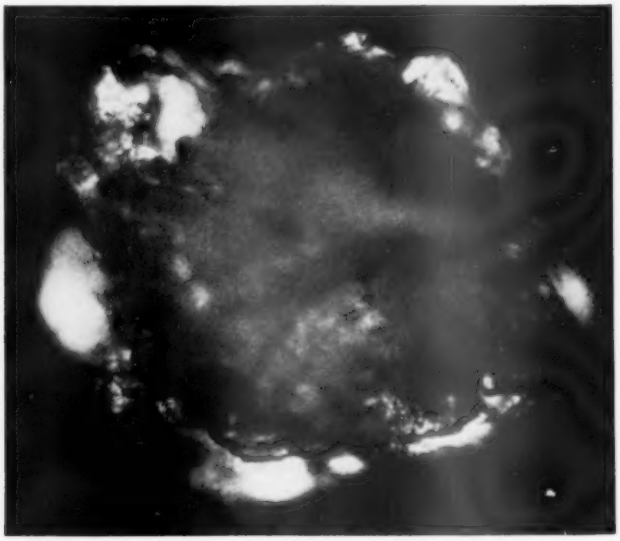

Fig. 5.

Fig. 4.—A gallstone's bristling irregular edges are well shown. The edges are composed of projecting crystals as shown in Fig. 5 (about ×30; reduced ⅕).

Fig. 5.—A single gallstone as viewed with partially polarized light. This shows the dense central crystalline mass with its border of projecting jagged irregular crystals (about ×60; reduced ⅕).

On cross section, the stones were found to be solid. The white gallstones usually appeared to be composed of a homogenous dense mass of pearly, glistening, translucent, platelike crystals. Some of the stones showed ringlike lamina-

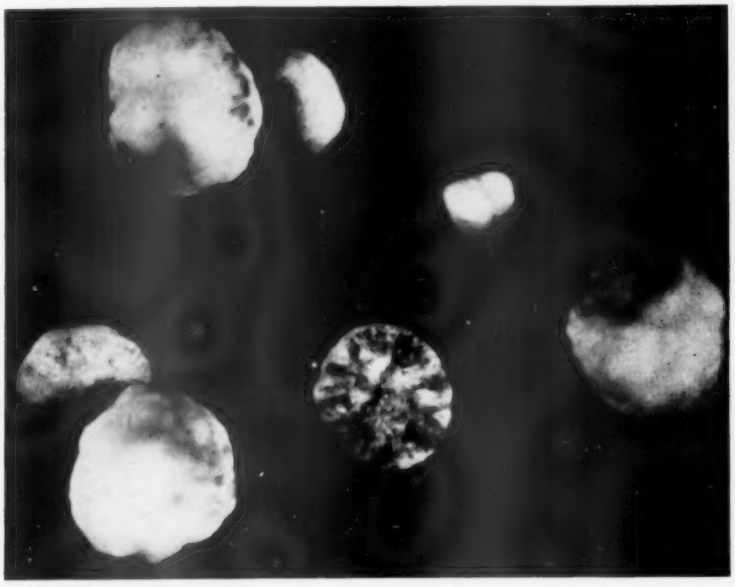

Fig. 6.—A cross section of a stone is shown in the central portion of the figure. The ringlike laminations are evident (about ×20; reduced $\frac{1}{5}$). The stones were obtained from one gall bladder, and weighed 2.0 mg. and contained 1.12 mg. (56 per cent) of cholesterol.

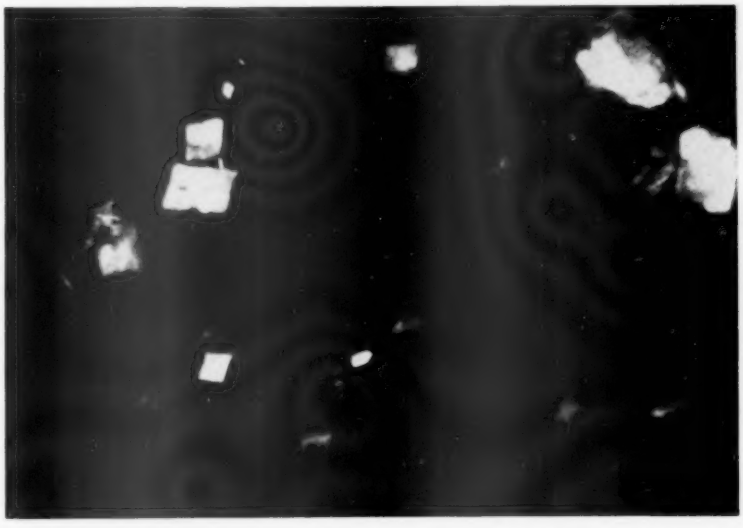

Fig. 7.—Isolated and aggregated crystals in a matrix of mucoid material

tions surrounding a central mass which was similar to the previously mentioned gallstones (Fig. 6). The yellow stones seemed to show this lamination more commonly than did the white ones.

Myriads of tiny, glistening, needlelike crystals and white, irregular particles of varying sizes were frequently associated with the stones. With magnification, most of the crystals appeared to be very similar to those present

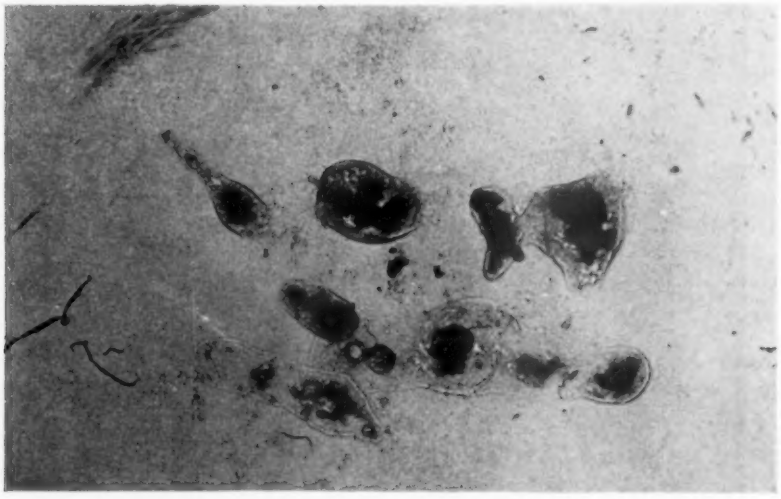

Fig. 8.—Gallstones embedded in gelatinous mucoid material.

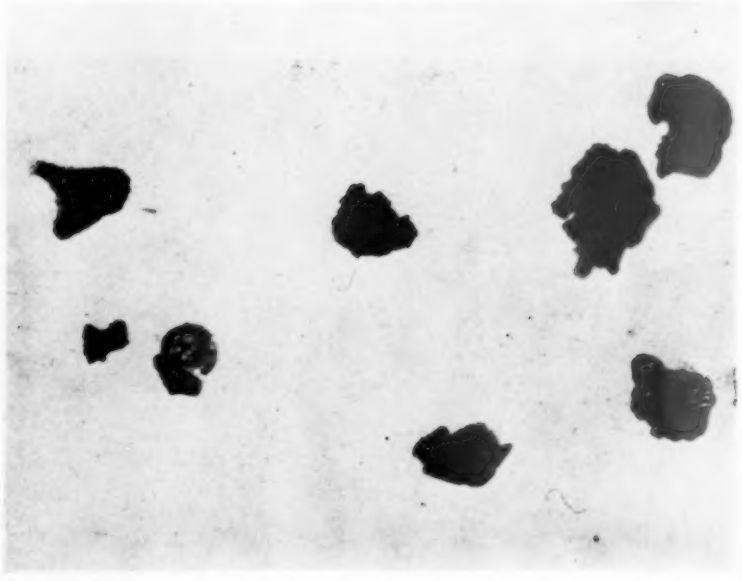

Fig. 9.—Black gallstones. The aggregated stones weighed 0.9 mg. but contained no cholesterol.

in the gallstones and were presumably cholesterol crystals (Fig. 7). Such crystals were sometimes found in the bile of gall bladders which contained no stones.

The figure number, weight, and cholesterol content of several gallstone specimens are listed in Table II. The cholesterol determinations were made by the method of Schoenheimer and Sperry,[3] with minor modifications. The cholesterol content of these stones ranged from 48 to 92.8 per cent of the stones' mass.

TABLE II

STONES' WEIGHT (MG.)	MG. OF CHOLESTEROL	PER CENT CHOLESTEROL
2.0 (Fig. 6)	1.12	56.0
2.0 (Fig. 3)	0.96	48.0
2.1 (Fig. 2)	1.5	70.8
0.7 (2 white gallstones)	0.65	92.8

Many of the stones and crystalline forms were embedded in an amorphous, translucent mucoid mass which frequently occupied most of the gall bladder lumen (Fig. 8). This material could be of importance in gallstone formation, for it might act as a barrier to prevent the crystals from being carried away by the flow of gall bladder bile prior to their aggregation as gallstones.

The mucoid material appeared to be secreted by the epithelium of the gall bladder. It was found in a majority of animals which were fed the test diet as well as in those fed the standard laboratory diet. It was present as an amorphous mass, as semiformed globules of clear, pale brown, or green-tinged material, or as soft, dark brown, formed, multifaceted masses. Varying amounts of black pigment were present on the surface of some of the latter. This could represent a stage in the formation of the black flakes or stones which were occasionally found (Fig. 9). Cholesterol was not found in several samples of black stones. Bluish green flakes were seen in the bile of a few animals.

SUMMARY AND CONCLUSIONS

This preliminary report confirms the finding of Dam and Christensen that gallstones were formed in Syrian hamsters which were fed a nearly fat-free test diet. An increased incidence of gallstone formation was observed in animals whose diet was deficient in either vitamin A or D. The increased incidence of gallstones formed in animals of the vitamin A-deficient experiment is statistically significant. The increased incidence of gallstones observed in animals of the vitamin D-deficient group is suggestive, but not statistically significant in the number of animals studied. Gallstones were not found in hamsters fed a standard laboratory diet.

Most gallstones appeared to be composed principally of crystalline cholesterol. The gallstones and associated crystals were frequently embedded in a gelatinous, mucoid mass, which was present in the lumen of the gall bladder. This admixture may be of importance in the genesis of gallstones. The cholesterol of the gallstones is obviously of endogenous origin and could be a result of a change in solubility or increased concentration of biliary cholesterol.

Until other studies are completed, further discussion of the various possible mechanisms involved in gallstone formation seems unwarranted. However, it is evident that there are now available an experimental animal and method suitable for the study of the mechanisms and the causative and modifying factors in the formation of gallstones.

I am indebted to Dr. Henry T. Randall, Dr. George W. Woolley, and Miss Madeline Stokem for valuable advice and assistance

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THE APPLICATION OF THE ENTEROHEPATIC CIRCULATION OF BILE ACID TO A STUDY OF THE PATENCY OF PORTACAVAL SHUNTS

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THE surgical treatment of bleeding esophageal varices has been undertaken with two fundamentally different approaches. In one, the varices are attacked directly by ligation or resection, and in the other, attempts are made to lower the elevated portal vein pressures which contribute to the distention of the esophageal varices. It is in this latter group that the use of a shunting procedure between the portal vein or one of its divisions and a systemic vein has been applied.

It is now eight years since Whipple and Blakemore[3, 27] reported ten cases with venous shunts which were performed with a vitallium tube technique. Within two years (1947) this technique was replaced by a direct suture anastomosis which has been applied in one of three types: end-to-side, side-to-side, or end-to-end. Mention should be made of a fourth method which is the interposition of a vein graft between the portal system and a systemic vein. The application of a particular type of shunt is variable and depends not only on the etiology of the portal hypertension but also on the preference of the surgeon. Our clinical experience has for the most part been with a side-to-side anastomosis between the portal vein and the inferior vena cava. For this reason, we have been interested in the postoperative patency of this particular type of shunt.

As a study preliminary to investigating the status of patients with shunts of several years' duration, we have applied the enterohepatic circulation of bile acid to dogs with portacaval shunts. The cycle of bile acid circulation from the liver to the small bowel via the bile duct and back up to the liver via the portal vein is extremely efficient in that little or no bile acid escapes from this cycle into the systemic circulation, which results in the bile acid concentration in the peripheral circulation being normally very low but constant. Introduction of a portacaval shunt can be expected to interrupt the cycle by diverting the bile acid absorbed from the bowel out into the systemic circulation. Such a diversion of bile acid should be made more apparent in the systemic veins by introducing exogenous bile acid into the enterohepatic circulation by oral feeding or duodenal intubation. Closure of a portacaval shunt should be accompanied by no rise in systemic bile acid following its introduction into the duodenum.

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METHOD

Medium-sized dogs were used as experimental animals. In one group of nine dogs, side-to-side portacaval anastomoses were constructed according to a method previously described.[18] In a second group of nine dogs, an Eck fistula was constructed by dividing the hepatic limb of the portal vein after side-to-side portacaval anastomosis. In selected cases, cholecystectomy and choledochostomy with cannulation of the proximal and distal ends of the divided common duct were performed subsequent to the shunt operation. Such cannulae were exteriorized on the abdominal wall and provided specimens of hepatic bile from the proximal catheter, whereas the distal catheter was a means of injecting cholic acid into the duodenum. In control experiments, cholecystectomy and choledochostomy were performed without the shunt operation in three dogs. In some of the experiments, cholic acid in capsules was administered orally with a small amount of meat. The status of the shunt was checked at the end of the series of experiments by sacrificing the animal.

In dogs, total bile acid is understood to include cholic acid for the most part and relatively smaller amounts of dehydroxycholanic acids. The determination of the total bile acid is by a photofluorometric method which was developed by Irvin in this laboratory.[12] The cholate in bile and blood was determined by a photometric method previously described which is specific for free and conjugated cholic acid.[13] In these experiments, the total bile acid and the cholate determinations can be regarded as having the same significance with respect to checking the patency of a shunt, and for this purpose the former method for total bile acid is preferable because of the smaller blood samples required. However, studies directed at the metabolism of cholic acid require the cholate determination.

RESULTS

1. The total bile acid concentration increased in the peripheral blood about five- to tenfold after duodenal administration of cholate in dogs with both types of shunt. The amount of cholate administered was 100 to 200 mg. per kilogram of body weight, and blood specimens were taken at thirty-minute to one-hour intervals and in some cases at five-minute intervals after cholate administration. The maximum concentrations occurred between 30 minutes and two hours after duodenal administration (Figs. 1 and 2). This was true in nine experiments using side-to-side shunts and nine experiments using Eck fistulas. The relationship between the dose administered duodenally and the elevation of the total bile acid in peripheral blood is demonstrated in an Eck fistula dog (Fig. 3). In most cases, however, when the cholate was administered in one dose in an oral capsule, the maximum total bile acid concentration in the peripheral blood was delayed in its occurrence and occasionally the elevation was slight. Nineteen experiments were observed and the delay or absence of peripheral blood total bile acid rise is attributed to the slow rate of cholic acid absorption in the duodenum.

2. In one experiment, an increase of cholate in the peripheral circulation was also observed after administration of cholate into the duodenum by injec-

tion into the cannulated distal ductus choledochus (Fig. 4). This rise in cholate was comparable to that noted for total bile acid and followed the injection of a like amount of cholic acid in the duodenum.

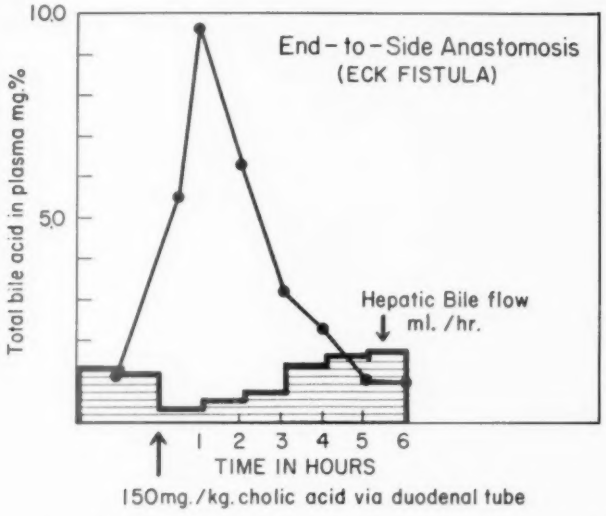

Fig. 1.—The relationship of total bile acid in the plasma and hepatic bile flow in the Eck fistula dog after duodenal administration of cholic acid.

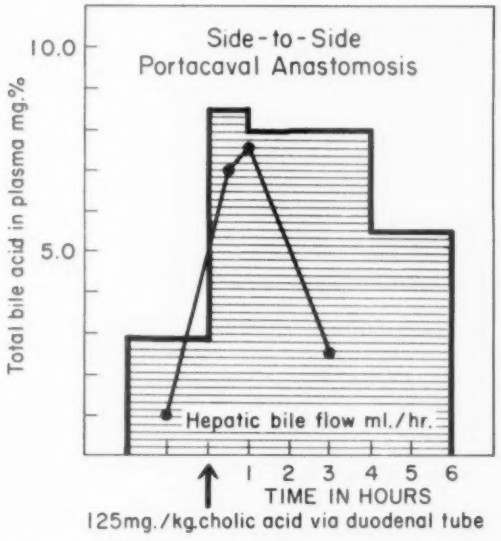

Fig. 2.—The relationship of total bile acid in the plasma and hepatic bile flow in a dog with a side-to-side portacaval anastomosis after duodenal administration of cholic acid.

3. Fig. 5 shows the elevation of the total bile acid in the peripheral circulation when the animal was tested several days after the shunt operation. Ten such experiments were observed.

4. In two animals, there was no increase in the total bile acid in the peripheral blood after administration of cholate (Fig. 6). Closure of the shunts

was demonstrated by sacrificing both of these animals. The specimen from the former is shown in Fig. 7.

5. In the five control experiments, cholate was again given duodenally. The marked increase of the bile acid in the peripheral circulation which was found in shunted dogs was not observed.

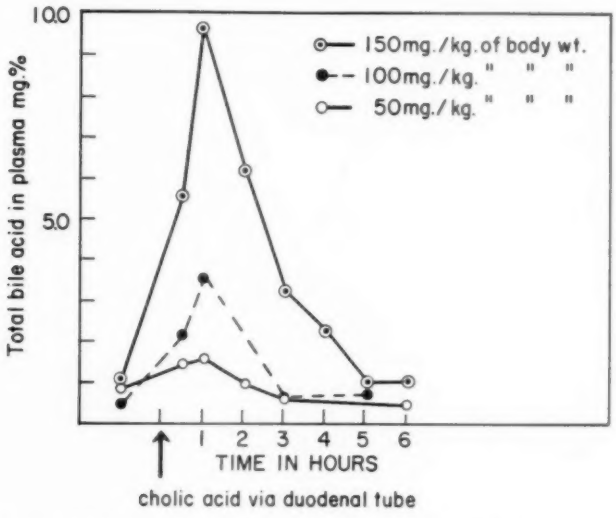

Fig. 3.—Peripheral total bile acid elevations in an Eck fistula dog following duodenal administration of different amounts of cholic acid.

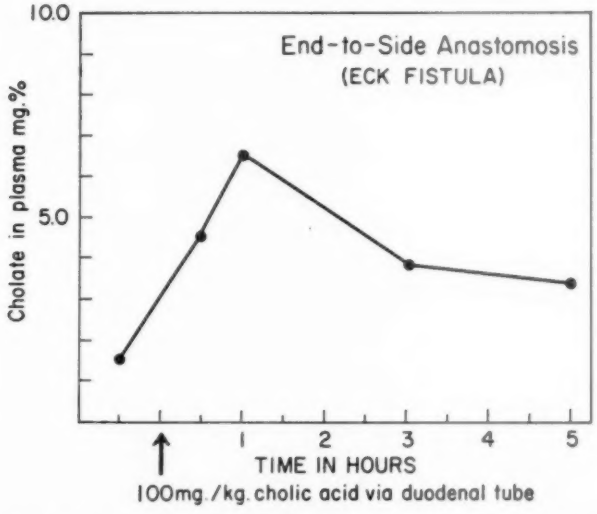

Fig. 4.—The relationship of cholate in the plasma after duodenal administration of cholic acid in the Eck fistula dog.

DISCUSSION

The patency of a portacaval shunt following operation has been evaluated using widely different methods. The direct measurement of the portal vein pressure by venipuncture at the time of operation before and after completion

of the shunt[3] has indicated significant decreases in portal hypertension after shunting. Manometric studies on the varices visualized through an esophagoscope have also been reported.[2, 21]

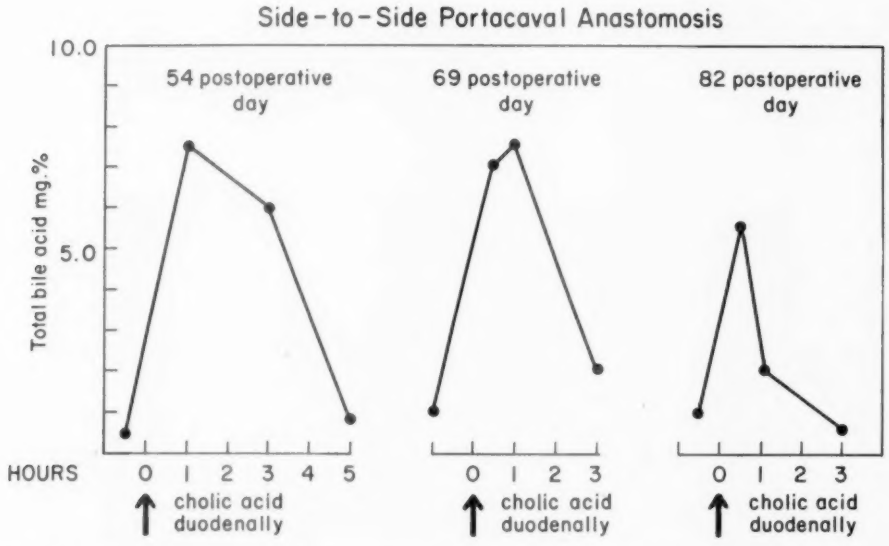

Fig. 5.—Peripheral total bile acid elevations in shunted dogs which were tested at different time intervals after the shunt operation.

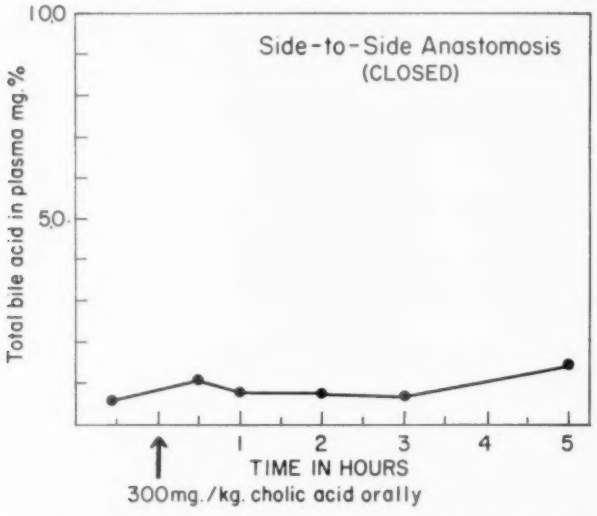

Fig. 6.—Failure in peripheral total bile acid to rise after duodenal administration of cholic acid in a dog with a closed shunt.

Venography demonstrating patent shunts has been accomplished by catheterization of the inferior vena cava and retrograde injection of the shunted portal vein.[8] Venography has also been accomplished by portal venipuncture at the time of operation[27] as well as by splenic puncture following operation.[6, 9]

The passage of quantitatively determinable substances through the shunt has likewise been used. Glucose has been given orally, and its immediate rise

in the circulation at the site of the shunt has been detected in a specimen obtained from the catheterized inferior vena cava.[1] Regional heparinization through a plastic tube left in the inferior mesenteric vein at the time of the shunt operation provides an evaluation of the shunt by determination of the clotting time and oxygen content in the blood passing through the shunt. The clotting time is noted to be prolonged in blood samples obtained by catheterizing the inferior vena cava and, similarly, the elevation of the oxygen content of blood from the inferior vena cava indicates the addition of portal blood through a patent shunt.[4]

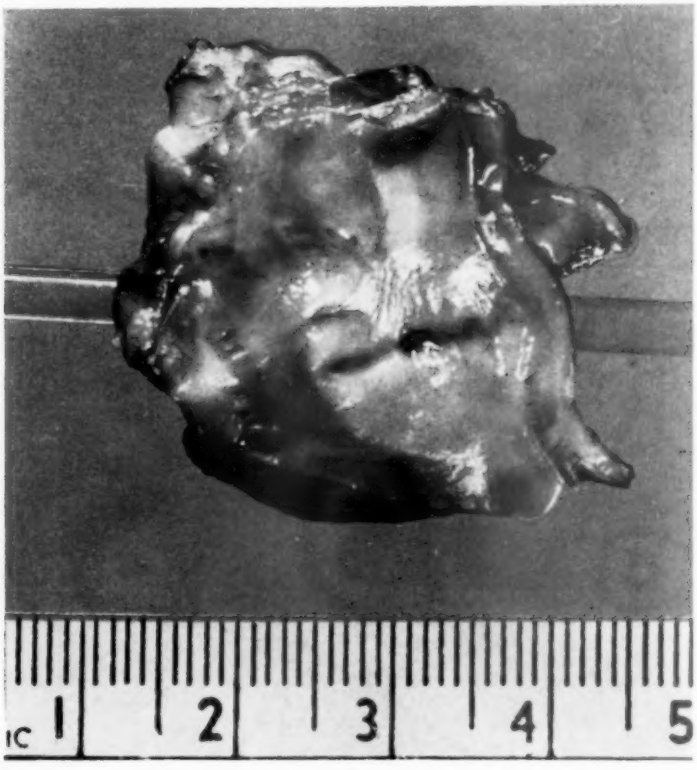

Fig. 7.—Photograph of the opened inferior vena cava of the dog presented in Fig. 6. The glass rod is in the portal vein and the closed suture line of the shunt is perpendicular to and between the autopsy clamp marks.

Application has been made of the shortened portal circulation time which occurs after a shunt. Ether has been administered rectally and the shunt evaluated by noting the rapidity of olfactory detection on the part of the subject.[7, 10] Similarly, dyes such as methylene blue and Congo red have been given orally and intravenously.[25] The time interval for kidney excretion following oral administration is comparable to the time interval for kidney excretion following intravenous administration after the shunt. Small amounts of bile acid have been administered orally to one patient following catheterization of the inferior vena cava at the time a splenorenal shunt was constructed.[19] Unfortunately, the dose was very small and the time intervals for sampling were such that the observations were not highly significant.

Finally, a clinical evaluation of the shunted patients has presented indirect evidence that the shunts remain patent, in that after a shunt, the severity and mortality of bleeding from esophageal varices are decreased.

It is well known that most of the bile acid which is given via the duodenum is absorbed into the portal system since the increase of bile acid in the portal blood after administration of the bile acid has been observed.[11, 16] On the other hand, under normal circumstances the increase of bile acid in the peripheral blood occurs to only a slight extent, if at all, after the administration of bile acid into the duodenum.[14] This holds true even if relatively large doses such as 0.2 Gm. per kilogram of body weight are given in dogs. The exception occurs under some pathologic conditions such as posthepatic jaundice.[14, 15] These facts suggested to us that if the portacaval shunt is constructed and the portal blood flows directly into the peripheral circulation through the shunt, the bile acid in the peripheral blood may increase after the administration of bile acid into the duodenum. Bile acid injected into the peripheral circulation disappears very rapidly under normal conditions although the exact mechanism is not understood, and in such circumstances, no peak in the curve of absorption will be observed.[5, 17, 20, 23, 24] However, in the shunted animal we can expect to observe the peak of the elevation of the bile acid in the peripheral circulation, because the removal of bile acid from the blood is not immediate.

The increase of bile acid in the peripheral circulation after its administration to the animal with potracaval anastomosis or Eck fistula depends upon the following factors:

1. The rate of absorption of bile acid from the intestine.
2. The functional patency of the shunt.
3. The rate of disappearance of the bile acid from the blood which is accomplished by excretion by the liver and possibly by other means such as a diffusion of bile acid into the tissues or fixation in the vascular wall.

On the other hand, when the elevation of bile acid is not observed in the peripheral circulation in the animal with portacaval anastomosis, it should suggest the following possibilities:

1. The shunt is closed.
2. The shunt is open, but most of the portal blood does not flow through the shunt.
3. The shunt is open, but the absorption of bile acid from the intestine is insufficient to cause an elevation in the peripheral blood.
4. The rate of disappearance from the peripheral circulation is very rapid compared with the rate of absorption from the intestine.

Following duodenal absorption of exogenous bile acid, the normal liver responds to this choleretic stimulus, and increased hepatic bile flow is evident. Such a rise in hepatic bile production indicates that the bile acid absorption in

the duodenum is sufficient to give increased values in the portal blood. It follows that if a shunt is open, detectable values in the peripheral blood may be present.

It is known that the liver function in an Eck fistula dog is decreased as compared with an animal with a side-to-side anastomosis.[22] In our experiments, elevation of the bile acid in the peripheral circulation in the Eck fistula dog remained high and indicated adequate absorption from the bowel. At the same time, the bile flow and excretion of bile acid in the bile remained low. This is compared to a relatively increased bile flow in the side-to-side shunt after bile acid administration. This seemingly indicated a failure of the Eck fistula liver to respond to the choleretic stimulus of the administered bile acid.

The slight sustained elevations of bile acid in the peripheral blood observed after the shunt operation without the administration of the cholate are noteworthy. This may well indicate a diversion of the bile acids from the enterophepatic circulation into the peripheral circulation or some degree of liver damage which follows the shunt operation. Similar elevations are found clinically after liver damage as occurs in cirrhosis or hepatitis.[26]

CONCLUSION AND SUMMARY

The elevation of the bile acids in the peripheral circulation after administration of the bile acids into the intestine indicates the functional patency of the shunt in the dog with side-to-side portacaval anastomosis or Eck fistula.

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SEGMENTS OF THE LIVER

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BOYDEN'S revolutionary studies on the segmental anatomy of the lung have caused surgeons to ask whether there may not be similar surgical segments in the liver. It might be desirable to perform operations with a minimum amount of bleeding and without the danger of depriving territories adjacent to the extirpated area of blood supply or drainage.

Data published in 1952[1] and 1953[2] may help to find an answer to the problem. The branches of the portal vein[1] and those of the hepatic artery[1, 3] supply sharply defined territories. So sharply defined, indeed, that a vinylite cast of the arterial and portal system is divided by deep clefts, bridged only in rare cases by small side branches. Since in the outlying portions of the liver, the hepatic ducts run alongside the portal veins and hepatic arteries, preoperative, stereoscopic cholangiography can give information on the exact boundary lines between the portoarterial territories. Incisions along the boundary lines can, therefore, avoid larger branches of the portal vein and of the hepatic artery.

However, the hepatic veins form a system quite independent of the portal tree:[1] Few of the hepatic veins run parallel to portal canals (Fig. 1). More frequently the hepatic veins cross them. The inferior root of the left hepatic vein crosses in front of the superior left ramus and the intermediate ramus and behind the inferior left ramus of the portal vein. The right hepatic vein crosses in front of the ascending ones among the central rami, the lateral ramus, and the inferior right ramus. Only some of the minor hepatic veins which enter into the vena cava at lower levels have courses more or less parallel to some minor portal branches. They are located in that inaccessible territory immediately adjacent to the vena cava. The drainage territory of the superior root of the left hepatic vein, however, is almost identical to the segment supplied by the superior left ramus of the portal vein.

The middle hepatic vein courses in the large plane which divides the distribution territories of the right and left trunks of the portal veins. It receives roots from the territories of the descending central rami and from the quadrate rami of the portal vein. Through this system of interdigitation, the human liver is made into one unified organ. It has this property in common with the liver of the orangutan, some ruminants, and the dolphin.[4] But it differs greatly from most other mammals, which possess distinctly multilobated livers. In these multilobated livers, major hepatic veins run parallel to major portal branches. Partial hepatectomy is, therefore, no problem in those animals.

The surgeon should, therefore, not only determine, by means of preoperative cholangiography, the boundaries of the portal segments, but he must also consider the course of the hepatic veins.

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Fig. 2 presents an attempt to map out surgical segments of the liver. Those territories in which no arrow is located must be considered indivisible units. This means that the entire right half is one surgical unit, that is, the extensive crossing of the afferent with the efferent vascular systems makes it impossible to find a portal segment which is drained by a single hepatic vein. In other words, if any part of the right territory is extirpated, degeneration of adjacent parts must be expected. The distal two-thirds of the superior left

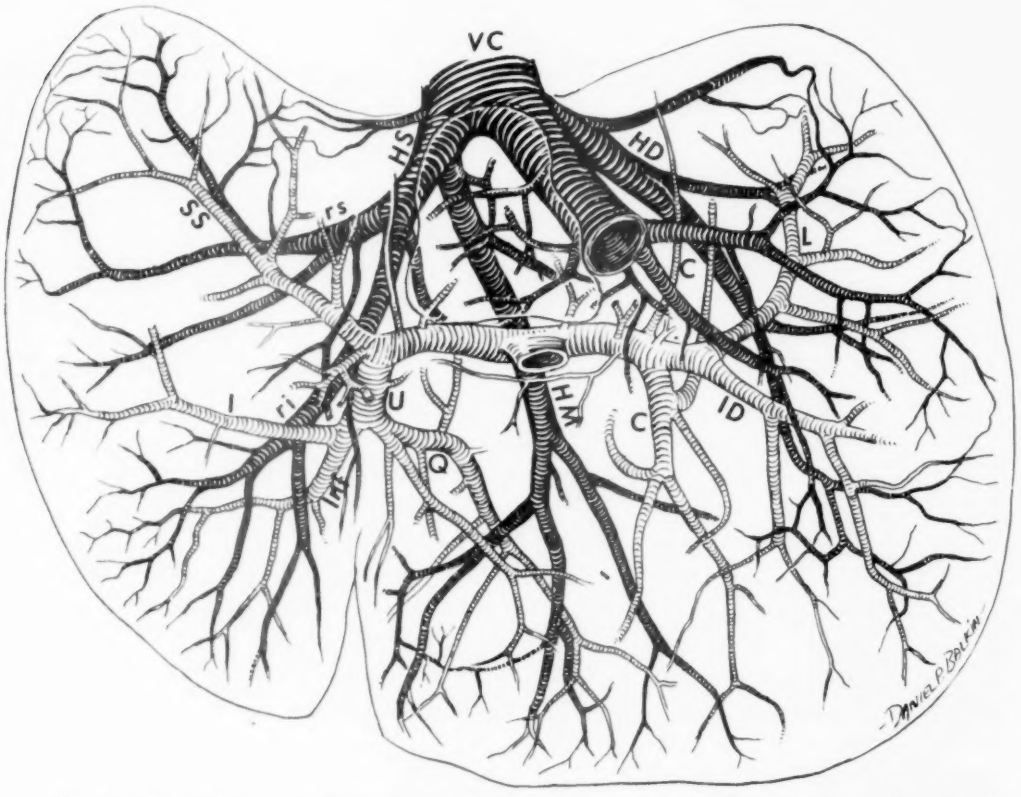

Fig. 1.—Corrosion preparation of a human liver injected with vinylite. Portal vein branches light, hepatic veins dark. Dorsocaudal aspect.

C = rami centrales venae portae
HD = vena hepatica dextra
HM = vena hepatica media
HS = vena hepatica sinistra
ri = its inferior root; *rs* = its superior root
I = ramus intermedius venae portae
ID = ramus inferior dexter venae portae
Inf = ramus inferior sinister venae portae
L = ramus lateralis venae portae
Q = rami quadrati venae portae
U = pars umbilicalis trunci sinistri venae portae
VC = vena cava inferior

territory, that is, the piece near the left triangular ligament, can probably be sacrificed without danger to any other part. This is also true for the inferior left and for the inferior quadrate territory. In the case of this latter, however, one should be aware that this territory is supplied by two or more medium-sized branches which arise at various levels from the wall of the umbilical part of the left trunk of the portal vein which runs downward in the ligamentum teres.

It must also be noted that the same territory is drained by several small hepatic veins which empty into the middle hepatic vein.

The caudate lobe (exclusive of its caudate process) is supplied by two small portal branches which run in a sagittal, dorsal direction, but it is drained by two small, horizontal hepatic veins. It is therefore indivisible, but largely independent of other territories.

If any of the territories in which an arrow is drawn is to be resected, the territory or territories to which the arrows point must also be sacrificed, since through the former run major vessels, draining or supplying the latter.

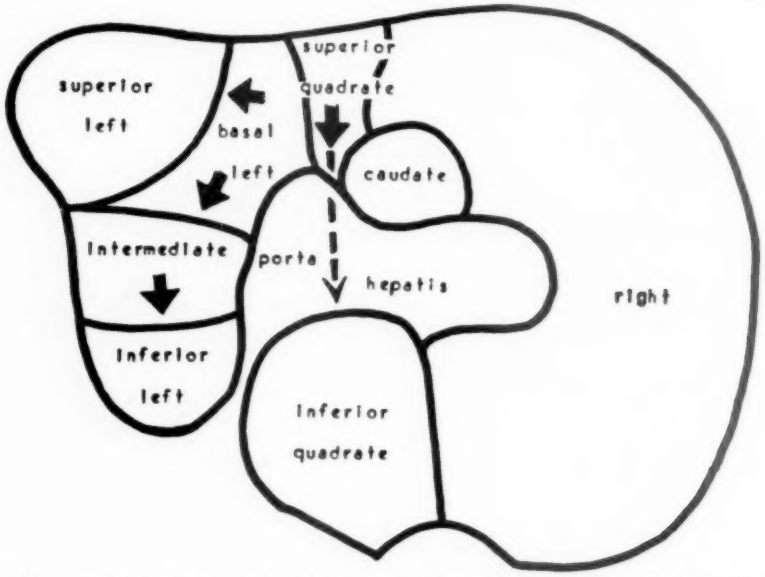

Fig. 2.—Human liver seen from behind and below showing suggested surgical segments. If a segment in which an arrow is drawn is resected, that segment to which the arrow points must also be sacrificed. Explanation in the text.

While in most of the parenchymatous portion there is strict coordination of the branches of the portal veins, of the hepatic arteries, and of the hepatic ducts, such coordination is not found in a large territory near the porta hepatis and the ligamentum teres.[1, 2] The three systems of the "portal triad" appear to be quite independent of each other in this region. Coordination begins approximately 0.5 cm. to 1 cm. distal to the origin of the named rami of the portal vein. Preoperative cholangiography is, therefore, useless for the prediction of the location of arteries and portal veins in the hilar area. It will, however, be useful in the parenchymatous areas of the liver.

SUMMARY

On the basis of recent studies on the gross anatomy of intrahepatic vessels and ducts, a suggested surgical anatomy of the liver is outlined.

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A SIMPLE TEST TO ESTABLISH THE PATENCY OF THE COMMON DUCT

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EXPLORATION of the common duct in the presence of multiple stones and chronic inflammation in the head of the pancreas is a rather trying procedure.

In attempting to establish the fact that the common duct is patent, one can be misled by the routine procedures which are now carried out. Routine cholangiography on the operating table is an ideal method but is not available in the vast majority of the institutions. Injection of fluid through a catheter with the resulting dilatation of the duodenum is a well-known and accepted procedure, but even this can be frequently misinterpreted. Probing may develop a false passage and, with it, a false sense of security that the duodenum has been entered.

It occurred to us during a rather difficult exploration that, in order to be certain that the common duct is patent, injection of a methylene blue solution through a catheter should yield a blue drainage from a Levin tube which had been previously inserted into the stomach and then carried through into the duodenum on the operating table. This test was so easily carried out and the results were so positive that we were amazed at its simplicity and thought it worth while reporting.

The steps in the procedure should be as follows:

1. A Levin tube should be inserted on the morning of the operation.
2. Before the common duct is opened, the Levin tube should be carried through the pylorus into the duodenum, so that the tip is in the region of the ampulla.
3. Needed surgery to the gall bladder and common duct should be carried out.
4. A catheter should be inserted into the distal segment of the common duct through the ampulla, if possible. A 20 c.c. sterile solution of methylene blue is then injected through the catheter, care being taken that it does not spill over into Morison's pouch, as this is rather messy.
5. The anesthetist now can apply suction to the Levin tube and the color of the material obtained can be observed. The presence of a blue dye establishes the patency of the duct but does not, of course, rule out residual common duct stones.

CONCLUSIONS

A simple means of determining the patency of the common duct is presented. It does not rule out the presence of common duct stones, but is valuable in establishing the fact that the channel explored is a patent common duct and not a false passage.

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EVALUATION OF THE CORTICOTROPHIN-EOSINOPHIL RESPONSE TEST IN SURGERY PATIENTS*

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ONE of the unsolved problems of preoperative evaluation of the surgical patient is the inability of the physician to predict the response of that patient to operation. This uncertainty continues to exist even after careful preparation, much of which is intended to increase the tolerance of a patient to a usually predictable magnitude of operative stress. Although it is appreciated that the adrenal cortex plays an important role in body homeostasis and consequently must contribute to the ability of an individual to withstand operative trauma, the level of adrenal cortical activity permitting the best response to operation is unknown. In an attempt to relate adrenal function to the outcome of an operation, the initial preoperative eosinophil count and the four-hour eosinophil response to a standard small test dose of corticotrophin were studied in 315 unselected surgical patients admitted to the University of Michigan Hospital. This approach was selected to permit an evaluation of the four-hour corticotrophin-eosinophil response test (Thorn test[1]) as a screening procedure in providing information of prognostic value regarding the response of patients to a variety of disease states and to subsequent operative trauma. The basal eosinophil count permitted an estimate of the degree of spontaneous pituitary-adrenal activity resulting from the illness, hospitalization, and anticipated operation in the patients studied. The response to a small standardized dose of corticotrophin indicated to a degree the responsiveness of the individual's adrenal cortex to stimulation. An important source of error in previous attempts to evaluate group differences in adrenal responsiveness, employing this test, has been the variability in the potency of the corticotrophin used. This cause of inaccuracy has been minimized in the present study by carrying out human bioassay of all of the corticotrophin lots used. The results obtained with lots found to be substandard in potency have not been included in the analysis. In addition, when possible, the significance of a subnormal response to the standard test dose was evaluated by means of a subsequent six-hour intramuscular test with a therapeutic dose of long-acting corticotrophin of the standard potency.

METHODS

Of the 315 patients included in the analysis, 189 (60 per cent) were males and 126 (40 per cent) were females. The age range was 13 to 94 years with a

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median age of 54 years. The tests were performed throughout the day while the patient was involved in the normal routine of a surgical ward. The initial eosinophil counts were obtained prior to a meal, and the following meal was delayed until the four-hour specimen was obtained. The test was not made on a day on which stressing diagnostic procedures were being carried out. This liberty in performance of the test was taken because, in practical application, many situations could prevent accomplishing it under more rigidly controlled conditions. In the majority of studies ACTX-corticotrophin ("corticotrophin, purified," "high-potency corticotrophin," "corticotrophin A") was used rather than ACTH-corticotrophin ("corticotrophin, crude," "U.S.P. corticotrophin") to increase the reliability of the standardized test, since only a small and probably variable portion of the latter preparation ever reaches the adrenal cortex.

Eosinophil counts were accomplished with the macrodilutional technique. A solution of 0.05 per cent phloxine in 50 per cent propylene glycol served as the staining solution. One to two milliliters of venous blood was drawn from a forearm vein under a tourniquet and placed in a tube containing a dry balanced oxalate anticoagulant (1.2 Gm. per cent ammonium oxalate and 0.8 Gm. per cent potassium oxalate). Two-tenths milliliter of thoroughly mixed oxalated blood was added volumetrically to 3.8 ml. of staining solution in a clean Kahn tube and gently agitated for three minutes by hand. Individual specimens were refrigerated at this point to permit counting at a convenient time without interfering with the schedule of simultaneous tests. Contact of the blood with the stain for at least ten minutes was assured prior to the actual counting, and thorough mixing of the cells was repeated. A Levy chamber 0.1 mm. deep was employed, and the cells in 1.8 ml. were counted. Those patients whose initial eosinophil count was 50 cells or less per milliliter of blood were excluded from the analysis correlating the test response with toleration of the operative procedure.

The responses to 12.5 and to 25 U.S.P. units of crude ACTH were obtained to provide a basis for comparison with the response to 8 U.S.P. unit doses of the different lots of purified corticotrophin.

RESULTS

Spontaneous Pituitary-Adrenal Activation in Surgical Patients.—Table I compares the initial eosinophil counts in groups of patients whose disease necessitated operative intervention with those observed previously in normal adults and in groups of patients with corticoid-sensitive disorders. In our results there is little evidence that the human pituitary-adrenal system is activated significantly by diseases requiring operative intervention. Patients with diseases of the prostate gland appear to represent an exception, but the low median count observed in these groups is possibly a reflection of lower urinary tract obstruction, urinary tract infection, and secondary effects on renal function, and consequently is not of any real prognostic assistance.

Four-Hour Response to 25 Physiologic Units of Corticotrophin.—The procedure and results of the human bio-assay of the lots of ACTX-corticotrophin

are reported elsewhere by Wolfson.[2] His report indicates that the responses to 8 U.S.P. units of satisfactory ACTX are statistically indistinguishable from the responses to 25 U.S.P. units of standard aqueous crude ACTH. Both induce responses approximating 25 intramuscular physiologic units of activity. The employment of 8 U.S.P. unit doses of a satisfactory lot of ACTX proved to be a feasible and consistent method of performing the four-hour test.

TABLE I. INITIAL DIRECT EOSINOPHIL COUNTS IN UNTREATED PATIENTS

	NO. OF SUBJECTS	MEDIAN 50% OF CASES		NO. OF SUBJECTS	MEDIAN 50% OF CASES
Normal Subjects	49	180	Surgical Data		
			Cancer of colon	15	189
Corticoid sensitive diseases			Cancer of stomach	12	155
Active allergic disorders	9	1,000	Cancer of breast	10	144
Active rheumatoid arthritis	45	210	Cancer of lung	27	222
			Cancer of prostate	9	89
Interval gout	23	185	Benign prostatism	25	133
Minor metabolic disorders	14	180	Peptic ulcer	14	183
Acute gouty arthritis	22	165	Gall bladder disease	19	167
Chronic eye diseases	11	150	Pneumonitis	17	155
Acute eye diseases	18	140	Arteriosclerotic vascular disease	20	244
			Uncomplicated hernia	15	189
			Nodular thyroid	12	127

Of the 315 patients receiving either the crude ACTH or the ACTX, 258 (81.9 per cent) showed a 50 per cent or greater fall in eosinophils after four hours, while fifty-seven (18.1 per cent) had an unsatisfactory response to the single test. There was no evidence that advancing age produced a change in responseness. Table II records the data on the 127 (40.3 per cent) subjects who were less than 50 years of age and 188 (59.7 per cent) subjects who were 50 years or older. It is evident that there was no difference in the percentage of patients showing a satisfactory or unsatisfactory response in the two age groups.

TABLE II. COMPARISON OF RESPONSE TO TEST IN SUBJECTS UNDER AND OVER 50 YEARS OF AGE

TOTAL PATIENTS 315	OVER 50 YR. 188	UNDER 50 YR. 127
Those having a 50% or greater fall in eosinophils	154 (81.9%)	104 (81.9%)
Those having a less than 50% fall in eosinophils	34 (18.1%)	23 (18.1%)

The Degree of Unresponsiveness in Patients With a Subnormal Response to the Test Dose.—Ten patients showing an unsatisfactory response to a test dose of corticotrophin were retested with a therapeutic dose of 35 units of ACTX. On the basis of calculated potency, the lot employed in retesting was substandard, supplying 73 units of physiologic activity, when compared with the Armour standard crude ACTH. However, this was three times the activity provided by the standard test dose. As shown in Table III, two of the ten patients failed to have a satisfactory fall in eosinophils upon retesting, but the

failure of response was not followed by any difficulty during the ensuing operation. The satisfactory outcome in eight of the ten patients following the administration of 35 units of ACTX emphasizes the importance of knowing the relative potency of the lots of ACTX to permit evaluation of dose-response relationships.

TABLE III. RESULTS OF RETESTING WITH THERAPEUTIC DOSE OF ACTX

PATIENT	SEX	AGE (YR.)	EOSINOPHIL FALL WITH TEST DOSE (%)	EOSINOPHIL FALL AFTER 35 U. 84666			INITIAL COUNT	DIAGNOSIS	OPERATION	TOLERATION
				4°	6°	8°				
1	M	41	21	10	55	20	111	Chronic empyema, non-t.b.	Yes	Good
2	M	54	0	0	45	66	201	Pulmonary t.b.	No	----
3	F	76	12	69	94	100	101	ASPVD-diabetes, gangrene	Yes	Fair
4	M	73	31	73	95	100	421	Ca of esophagus	No	Cardiac arrest*
5	M	70	13	0	80	100	111	ASPVD gangrene	Yes	Good
6	M	50	37	50	56	80	278	Ca of lung	No	----
7	M	16	0	62	88	92	555	Constrictive pericarditis	Yes	Good
8	M	45	33	67	93	100	167	Buerger's disease	Yes	Good
9	M	23	33	59	59	56	355	Gastric ulcer	Yes	Good
10	F	71	58	52	77	97	2,671	Esophageal stricture	No	----

ASPVD = Arteriosclerotic peripheral vascular disease.
*Patient not included in final analysis because initial test performed with an unsatisfactory lot of ACTX.

Correlation of the Four-Hour Corticotrophin-Eosinophil Response Test With Observed Toleration of Operative Procedures.—One hundred ninety-three (61.3 per cent) subjects underwent an operation following the test, while 122 (38.7 per cent) patients did not have an operative procedure during the period of hospitalization when the testing was being carried out. Of those having operations, 163 (84.5 per cent) showed a satisfactory response to the test, while thirty (15.5 per cent) did not have the required 50 per cent or greater fall in eosinophils. On the other hand, of those who did not undergo an operation, ninety-five (77.8 per cent) responded satisfactorily to the test dose of corticotrophin, while twenty-seven (22.2 per cent) exhibited an unsatisfactory response. All the patients in the operative group had a general inhalation anesthetic for procedures ranging in magnitude from simple breast biopsies to radical thoracoabdominal operations. The events of the operative period were evaluated by examination of the anesthetic record. It is recognized that a multitude of factors must be considered when attempting to interpret the course of a patient during an operation. Furthermore, the criteria that constitute an important departure from the expected or accepted reactions of the anesthetized patient are not uniform. For the purposes of this report, arbitrary criteria of an unsatisfactory operative course were selected. These included: (1) a fall in systolic blood pressure to 90 mm. Hg or below for preoperatively normotensive patients, or to 100 mm. or less for hypertensive patients, which lasted for fifteen minutes or longer, (2) the development of a cardiac arrhythmia with a fall

in blood pressure, and (3) the development of cardiac arrest. One patient had a cardiac arrest during the operation, which was a cardiopectoraloplasty for incapacitating coronary artery disease. He had responded to the test dose of corticotrophin preoperatively with a 67 per cent fall in total eosinophils in four hours. Of the 163 patients having an operation following a satisfactory test response, thirty-two (19.6 per cent) had some difficulty during the operative period, and three of the thirty patients who did not respond satisfactorily had an untoward event. Analysis of the data by means of the chi square test did not reveal any significant difference between the two groups in the incidence of undesirable episodes arising during operation. Also, as shown in Fig. 1, there was no evidence to suggest that there had been an inadvertent selection of patients in so far as their response to the primary disease was concerned since the initial eosinophil counts for the two groups showed a similar distribution, with the majority falling within the range of normal.

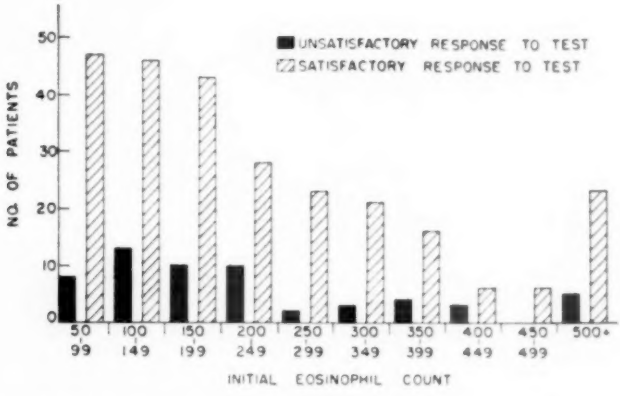

Fig. 1.—Comparison of the base-line eosinophil counts with the response to the test in subjects undergoing operation.

COMMENT

As the corticotrophin-induced eosinophil response test has been applied in the past few years, it has become evident that there are definite limitations in interpretation of the results. Our experience with the test as a routine preoperative measure has led us to feel that it has little practical value in helping the surgeon to predict the response of a patient to operation. It is recognized that when the clinical status warrants the consideration of existing or impending adrenal cortical insufficiency, valid conclusions about adrenocortical responsiveness can be reached by following the eosinophil response and measuring the urinary steroid excretion induced by stimulation with 100 units of physiologic activity of corticotrophin for at least two days after obtaining satisfactory base-line determinations.[3, 4] However, this extension of the test is not feasible for routine use because of the time involved and technical assistance required.

It has been appreciated that the response of circulating eosinophils is a sensitive, though limited, criterion of adrenal cortical activation. A number of investigators have observed a normal daily variation in eosinophil levels and

have reported the errors inherent in the counting methods employed.[5, 6] These investigations have led to some dissatisfaction with the reliability of the four-hour test, but it was felt that the macrodilution technique used in this study tended to minimize the errors associated with counting eosinophils.

In this experience with our surgical population, no instance of relative or absolute adrenal cortical insufficiency affecting the ability of a patient to withstand an operation was discovered by general application of the test. The data indicated that 18 per cent of our patients may have an undesirable episode arousing the concern of the operative team during an operation under general anesthesia, although the percentage having critical difficulty is much lower.

SUMMARY

Of 440 unselected consecutive patients admitted to the Surgery Service, 315 patients were submitted to a four-hour corticotrophin-eosinophil response test with a clinically potent lot of corticotrophin in the preoperative period. Analysis of the data obtained on these patients revealed little evidence that the stress of their disease, hospitalization, and the usual preoperative diagnostic procedures caused any appreciable spontaneous activation of their pituitary-adrenal system. The preoperative responses of 193 of these patients who were submitted to operation, after the standardized four-hour test, failed to show any significant correlation with the subsequent tolerance of an operation. Indeed, the clinical significance of the test appeared questionable since retesting of ten patients with larger doses of corticotrophin resulted in evidence of acceptable adrenal responsiveness in all instances, even though the response to the standard test had been poor.

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CONCERNING THE PROBLEMS OF A TISSUE COMMITTEE REVIEWING THE DIAGNOSIS OF ACUTE APPENDICITIS

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DUE to the widespread use of antibiotics, many of the problems of the treatment of appendicitis have become of academic interest only. The mortality has been brought to that irreducible minimum to be expected in any series of major operations. The morbidity has also been greatly improved with the reduction in postoperative complications due to infection. However, the problem of the diagnosis of acute appendicitis now has implications not previously considered important. With the recent and present publicity concerning "unnecessary surgery" and "unethical surgical practices," the emergency appendectomy needs very close scrutiny. Of all major operations performed, appendectomy is by far the most common and may represent as much as 40 per cent of the surgery performed in small hospitals.[1] So common is the operation of emergency appendectomy that it is cynically said that a patient need only complain of right-sided abdominal discomfort to find himself the victim of an emergency appendectomy. The American College of Surgeons has advocated the formation of "tissue committees" to audit the surgery performed and point the way to elimination of unnecessary surgery. The American Medical Association has appointed a committee to investigate the causes of "unethical practices." With all of this public interest and this activity toward self-discipline on the part of the medical profession, there is need to review the existing standards that might be used to judge reports or audits of staff activities. Also the criteria upon which an audit can be based need clarification. Experience has suggested that unnecessary surgery occurs most frequently in certain types of surgical procedures such as appendectomies and gynecologic surgery. Considering the voluminous literature on appendicitis, it is interesting that there is so little written concerning the accuracy of the diagnosis of acute appendicitis and that the confirmation of this diagnosis may rest on such a variety of pathologists' terms. Therefore, it is not surprising that there is little basis upon which to set an acceptable standard of "normal tissue removal" by emergency appendectomy.

It is the purpose of this communication to present the problems that confront a tissue committee in reviewing the validity of emergency appendectomies, to suggest certain criteria needed for such a review, and to give the results based on a previous ten-year survey (1935-1944)[2] augmented by an additional five-year survey (1947-1951) just completed. This report comes from a small (250-bed) private hospital functioning with essentially a closed staff. During the first ten-year period, six surgeons performed 95 per cent of the surgery. During the third five-year period, six performed 96 per cent, there being two losses and two replacements on the staff. During the third five-year period an

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intern-resident training program was established. In this fifteen-year period, 3,277 patients were treated for appendicitis, but 36 per cent underwent an "interval appendectomy" and so are of little interest to this study. A total of 2,071 patients were treated for suppurative appendicitis, with an over-all error in diagnosis of 20.6 per cent. This surgery comprised 8 per cent of the major surgery performed during this fifteen-year period.

On first consideration, a critical survey of emergency appendectomies would seem to be a very simple affair. The patient is admitted as an emergency, is operated on as an emergency for acute appendicitis, and either does or does not have acute appendicitis. If the survey could be conducted on such an elemental level, there would be no problem. Unfortunately there can be so many ramifications to such a survey that if a well thought-out plan is not made in the beginning, any possible information gained will be lost in the confusion of many technicalities. To aid any committee that might be considering a survey of emergency appendectomies in their hospital, certain classifications and terms will be discussed. At all times it must be remembered that the reason for the survey is to ascertain the number of "normal appendices" removed at an emergency operation for acute appendicitis. This number per individual operator is then to be compared to the accepted error in diagnosis for acute appendicitis. That there is little published upon which to base such a comparison is one of the problems. Thus Van der Hoff,[3] in a detailed study of 4,485 cases, felt that the diagnosis of acute appendicitis was certainly in error in 10 per cent of the cases and probably so in an additional 5 per cent, for a total error of 15 per cent, but this was only an opinion and not based on a pathologist's report. Reynolds and Goodof,[4] reporting on the accuracy of diagnosis of 141 cases, considered all deviations from a "normal appendix" as proof of acute appendicitis, but still found an error of 15 per cent. Gilmore and Lowdon,[5] in comparing the mortality of two groups of patients, incidentally mentioned that 6.7 per cent of the first group, and 14.5 per cent of the second group, had a normal appendix removed. There is no clarification of "normal appendix." Therefore, certain classifications and standards must be set up before the survey starts. They may seem to be most elemental, but experience will show that they are necessary.

1. What is an emergency admission? This is relatively simple except for those patients who have been seen in the outpatient department once or twice during the day of admission or once or twice a day for several days before the attending physician was convinced that they needed hospital care. In the survey here reported, those who were considered to have "continuing appendicitis" were placed in a separate category.

2. What is an emergency operation? In this survey those patients whose operation was delayed for more than twelve hours because of further laboratory work or consultation were placed in a separate group regardless of the pathologists' findings, and were not considered emergencies.

3. What is a "normal appendix" or, vice versa, what description by the pathologist confirms the diagnosis of acute appendicitis? It is all very well to

state that the final evaluation of any case is a clinical evaluation, but the initial screening and certainly the final decision in a doubtful case will be based on the pathologist's report. Many authors[3, 5, 6] failed to mention what has constituted simple acute appendicitis in their report other than the operator's impression, or have taken such a liberal view[4] that there can hardly be a "normal appendix." Although we admit that mechanical factors such as fecaliths and adhesive bands could cause abdominal pain severe enough to warrant emergency surgery, we have stood by the criterion of "suppurative appendicitis with purulent exudate in the lumen and pyogenic infiltrations of the wall" as necessary to confirm the diagnosis of acute appendicitis. Such terms as "catarrhal appendicitis," "lymphoid hyperplasia," "constrictive appendicitis," "active chronic appendicitis," "fecal appendicitis," "active recurrent appendicitis," "obliterative appendicits," and so forth, were considered synonymous with a normal appendix. This is a very rigid classification, but since in an appreciable number of cases the pathologists' report may be final, the tissue committee must set up its standards before starting a survey. We advocate this standard because it easily draws the line between the proved case and the doubtful case, and makes the proved case beyond doubt. Obviously all tissue removed must be sent to the pathologist, as his report is far more reliable than the operator's clinical impression. It is equally obvious that the tissue committee must understand the language of the pathologist.

These standards having been set up, the records of all patients for whom an appendectomy was performed as the primary procedure must be reviewed. In addition to this, the operating room records must be examined to include all cases with a preoperative diagnosis of acute appendicitis, as there will be an appreciable number of such cases in which the diagnosis was in error. To check the validity of emergency admissions and emergency surgery for appendicitis, these cases must be included. The results of this survey are offered with the hope that similar surveys will be made in all types of hospitals so that classifications and standards may be agreed upon to judge such surveys.

Table I shows the accuracy of diagnosis in each of the five-year periods surveyed:

TABLE I. ACCURACY OF DIAGNOSIS (ALL CASES OPERATED AS EMERGENCIES)

	1935-1939	1940-1944	1947-1951
Proved appendicitis	417	614	496
No appendicitis	93	93	96
Proved other disease	16	23	42
% Error	20.7%	15.8%	21.7%

In the "proved cases" are included the cases of simple acute appendicitis and appendicitis with peritonitis or abscess. The pathologists' finding of suppurative appendicitis with purulent exudate in the lumen was reported in all cases included as simple acute appendicitis. Those cases classified as "no appendicitis" were those in which the appendix was described as active chronic appendicitis, catarrhal appendicitis, and so forth. The error for each of the

five-year periods is noted. The over-all error of 20.6 per cent will probably be high if compared to other reports yet to be made, unless the same classification of simple acute appendicitis is used.

In considering the diagnosis of acute appendicitis, although the history, physical findings, and laboratory data have each been thoroughly examined, it is the composite picture that makes the diagnosis possible. A reasonably typical picture has been reported in as few as 61 per cent and as many as 90 per cent of the cases of proved appendicitis.[7] In the first report of ten years it was felt that 81 per cent of those patients operated on had a typical picture of acute appendicitis. In the third five-year period 75 per cent had a typical picture. In the group operated on as emergencies but for whom no suppurative appendicitis was reported, 71 per cent of patients in the fifteen-year survey had a reasonable picture of acute appendicitis. It is in this group that the "Disease X" becomes apparent. This disease is characterized by a history of generalized abdominal pain localizing to the right lower quadrant, nausea and vomiting, a well-elevated white blood count, slight elevation of temperature, and a normal urine. On examination, there are found tenderness and spasm in the right lower quadrant. Laparotomy reveals no pathology. The pathologist reports active chronic appendicitis, and the patient, relieved of his complaints, will sit up in bed the next morning and demand breakfast. This course of events takes place often enough to make any critical observer seriously question, "What was the disease so successfully treated by appendectomy?" The tissue committee looking for "normal appendices" removed as emergencies may wish to take into consideration "Disease X," which of course is apparent only if the chart has recorded a history, physical examination, and laboratory work carried out preoperatively.

What percentage of error is allowable and what percentage is excessive per operator need clarification by further reports and undoubtedly are open to regional variation. Also, the availability and nightly energy of each surgeon may vary, as well as his own philosophy concerning immediate operation versus observation. And that surgeon who has recently missed the diagnosis of acute appendicitis or had a "run" of ruptured appendices with atypical histories is more prone to emergency surgery. We offer Table II, which shows the diagnostic error of each operator, only as our individual record and not as a model of achievement. All patients were operated on as emergencies. Not included are those patients observed in the hospital for over twelve hours before surgery. Included as in error are those patients operated on for acute appendicitis but having another disease. As stated before, there are no figures presently available indicating an acceptable error. However, any marked deviation from the group average needs comment. Those groups of patients under 100 are too small to be statistically of importance, as the interpretation of four or five charts one way or the other will alter the percentage figures. In the larger groups of patients of Operators 1, 2, 3, and 5, the fifteen-year average is good despite our rigid classification of simple acute appendicitis.

The seriousness of failure to make the diagnosis of acute appendicitis is well known.[8, 9] Often this occurs because the patient is admitted on another

service, surgical consultation being obtained only after the disease is advanced. Table III lists those patients whose preoperative diagnosis was other than appendicitis or for whom the diagnosis of appendicitis was not made until the hospital course made this evident.

TABLE II. DIAGNOSTIC ERROR BY OPERATOR

OPERATOR	1935-1939 AVERAGE 20.7%		1940-1944 AVERAGE 15.8%		1947-1951 AVERAGE 21.6%		15 YEARS AVERAGE 20.6%	
	TOTAL CASES	% ERROR	TOTAL CASES	% ERROR	TOTAL CASES	% ERROR	TOTAL CASES	% ERROR
1	167	15.5	119	6.7	None		286	11.8
2	105	12.3	71	18.3	7	40.0	183	14.1
3	123	21.9	331	12.6	192	13.5	646	14.5
4	32	21.8	37	16.2	None		69	18.8
5	23	13.1	55	7.2	170	19.4	248	16.1
6	4	0.0	90	27.7	53	30.1	147	27.9
7	None		None		134	34.4	134	34.4
8	None		None		60	21.6	60	21.6
Others	50	26.0	35	11.4	15	26.6	100	22.0

TABLE III. PATIENTS OPERATED ON WITH OTHER DIAGNOSIS OR AFTER LONG DELAY IN MAKING DIAGNOSIS OF APPENDICITIS

	1935-1939	1940-1944	1947-1951
Cases	26	56	11
Deaths	2	2	1
Very difficult course	2	2	4

The seriousness of the missed or delayed diagnosis is obvious from the five deaths reported. The fear of the missed diagnosis is a real impetus toward emergency surgery, but the fear of rupture under observation is much stronger. However, many authors have advocated observation, repeated laboratory work, and consultation for the doubtful case.[9] This was done quite infrequently during the first ten-year period, but during the third five-year period (1947-1951), a group of 111 patients were admitted with the presumptive diagnosis of acute appendicitis. These were studied for an average of thirty-six hours and then operated on with the preoperative diagnosis of continuing appendicitis. Table IV shows the results in this group. There were no deaths, and only two patients had a more severe course because of this delay. Free rupture of the appendix did not occur under these circumstances. Therefore, in the doubtful case it would seem safe to delay operation for further study. Unfortunately we have no data concerning those patients observed and then discharged or later correctly treated for another disease.

TABLE IV. PATIENTS OBSERVED AND THEN OPERATED ON FOR APPENDICITIS, 1947-1951 (DELAY HARMFUL TO TWO)

Suppurative appendicitis found	60
No appendicitis found	42
Another disease found	9
	111

The differential diagnosis between acute appendicitis and other diseases has been well discussed. The eighty-one cases of other diseases found at emergency

laparotomy are not separately listed here. In defense of this error, perhaps fourteen of the eighty-one patients required emergency laparotomy for the proper treatment of the disease present. The tissue committee in reviewing such cases might well take into consideration those patients whose disease made laparotomy mandatory. We have included these cases as "in error"; another tissue committee might rule otherwise.

Finally, as a point to add to the confusion, of the patients having an interval appendectomy, 13.7 per cent were reported as having acute suppurative appendicitis—perhaps a reversal of "Disease X."

SUMMARY

To meet the criticism of "unnecessary surgery," the American College of Surgeons had advocated the establishment of tissue committees to review the work carried out in smaller hospitals and to check any unnecessary surgery. Experience has shown that unnecessary surgery occurs more frequently in gynecologic surgery and appendectomies. To date, little has been written concerning an acceptable error in the diagnosis of acute appendicitis, and so an acceptable rate of normal tissue removal by appendectomy.

In this communication, certain suggestions are offered to any tissue committee contemplating an audit of the authenticity of emergency appendectomies in their hospital. Classification and standards are discussed. The results of a fifteen-year survey are given whereby an error of 20.6 per cent was found in 2,071 patients treated for suppurative appendicitis. The per cent of error of each operating surgeon involved is given, to be used for comparison with other surveys. The danger of the "missed diagnosis" is again emphasized, but also it is pointed out that the doubtful case may be safely studied by consultation or further laboratory work. We would like to emphasize strongly that any such survey is not as simple as certain publications make it appear. If a carefully thought-out plan is not formulated before the survey starts, any information that might be gained will be lost in confusion. Before the implication is made that "unnecessary surgery" is being performed, careful consideration must be given to all facets of the problem.

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Case Reports

MUCOEPIDERMOID TUMOR OF THE PAROTID GLAND IN A 6-YEAR-OLD CHILD

Case Report

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THE term "mucoepidermoid" tumors of the salivary glands was coined by Stewart, Foote, and Becker[1] in 1945 to classify a certain group of rare tumors of these organs. In their publication, they critically analyzed forty-five cases of this type. Bernier[2] in 1946 presented three additional cases, and in 1952, Pung[3] added one other case.

According to the review of Stewart and associates, these tumors may be either benign or malignant. The sources of the tumors are apparently the ducts of the salivary glands, and the tumors may arise in any of the locations where salivary gland tissue is found. These were distributed in the cheeks, hard palate, tonsillar fossae, nasal cavity, alveolar ridge, and nasopharynx. We refer the interested reader to the review by Stewart and co-workers, for the histopathologic descriptions of the various types of these tumors. The youngest patient in their series was 7½ years of age.

The present case concerns a 6-year-old male child who was admitted to St. Mary of Nazareth Hospital on Jan. 8, 1952. The parents first noticed a swelling in the left parotid region six months previously and, because of increase in hardness of the tumor, consulted the family physician (A. R.). Physical examination revealed a freely movable, painless swelling in the left parotid area about the size of a marble (1 to 2 cm.). Examination of the neck, oral cavity, nose, and nasopharynx was negative for other masses. X-ray films of the head and neck were essentially negative.

On Jan. 15, 1952, under general anesthesia, a firm, localized nodule measuring 1.5 cm. in diameter was removed from the substance of the parotid gland. Microscopic examination revealed a mucoepidemoid tumor of the parotid gland (Fig. 1). The postoperative course was uneventful. In the latter part of February, 1952, it was apparent that recurrence had taken place, and the patient was readmitted to the hospital on Feb. 27, 1952. During this admission, the parotid gland was exposed under general anesthesia through a more extensive incision over the gland, and the lower two-thirds of the structure was removed. A few of the lower branches of the facial nerve were sacrificed. Exposure of the upper division of the facial nerve appeared to be grossly free of tumor. Accordingly, it was not detached. Microscopic examination of this tissue again showed mucoepidermoid carcinoma invading the parotid gland (Fig. 2). The postoperative course was uneventful, and the patient was sent home on March 5, 1952, presenting at this time only a slight drooping of the corner of the left side of the mouth but without any other findings. A few weeks later, it was again apparent that a recurrence was developing in the upper remainder of the parotid gland.

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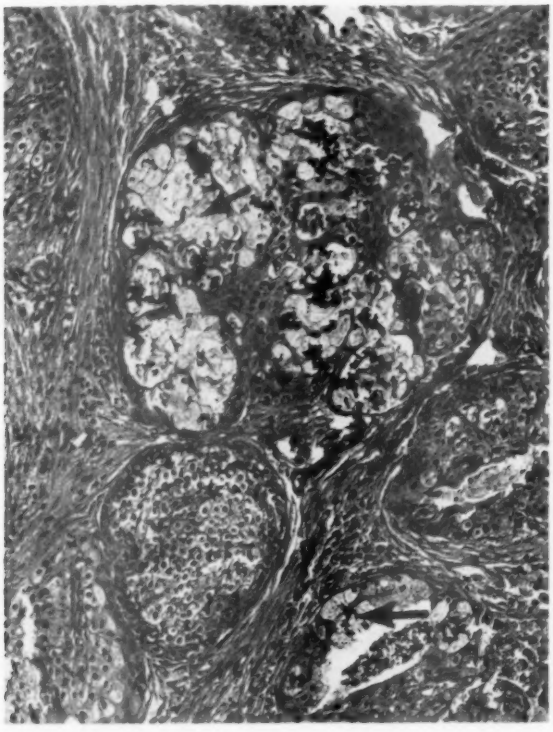

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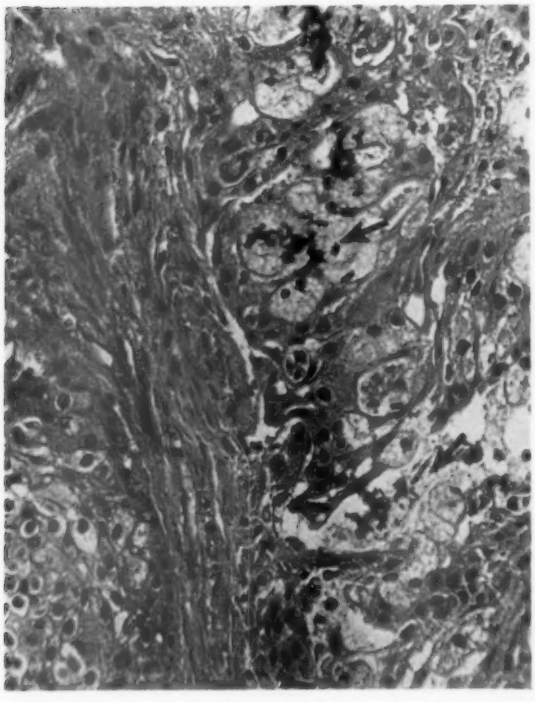
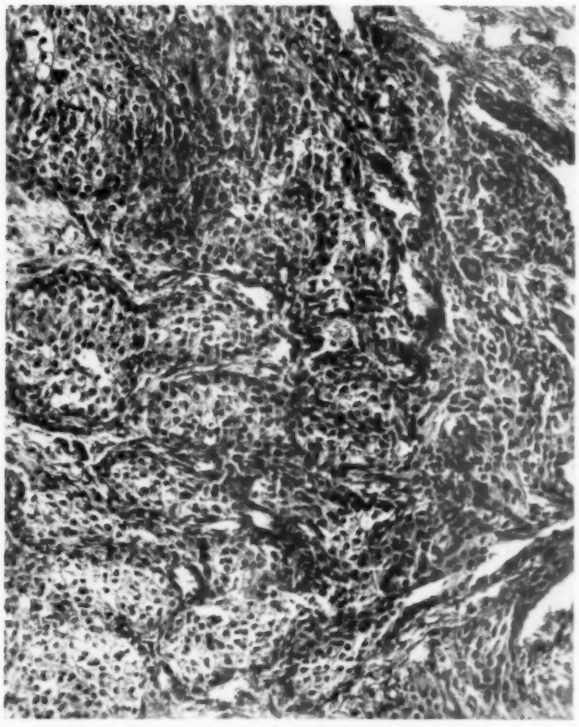


B.

Fig. 1.—*A*, Low-power view of the parotid tumor removed at the first operation. Epidermoid cells and mucin (shown by arrows) were uniformly scattered throughout the tissue. The presence of mucin was demonstrated in all sections with appropriate stains. (×150; reduced ⅙.)

B, Higher power view of *A*. (×300; reduced ¼.)



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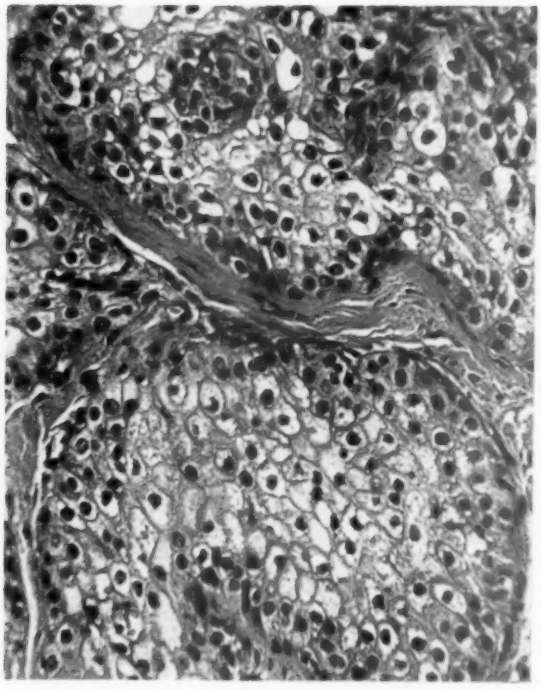
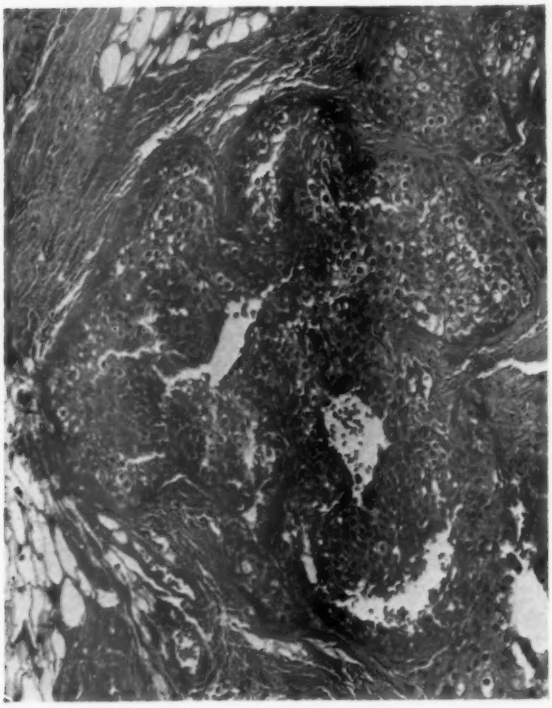
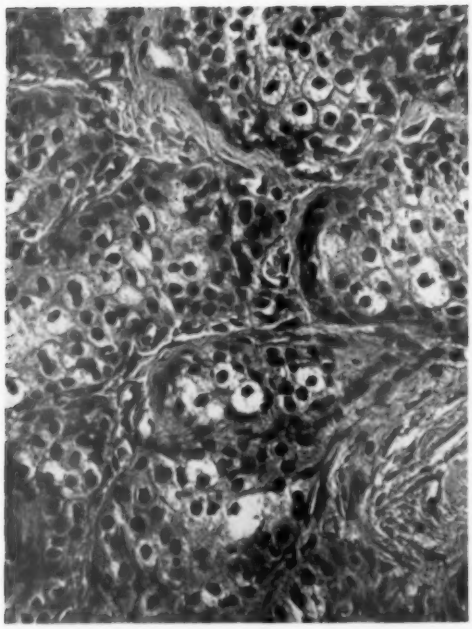


B.

Fig. 2.—*A*, Low-power view of parotid gland showing recurrence of tumor at the second operation. Mucin production was very slight as in Fig. 3. (×150; reduced ⅕.)
B, Higher power view of *A*. (×300; reduced ¼.)



A.



B.

Fig. 3.—*A*, Low-power view of nest of epidermoid elements in upper portion of parotid gland removed at the third operative procedure. (×150; reduced ⅕.)
B, Higher power view of *A*. (×300; reduced ¼.)

Accordingly, the patient was again readmitted on March 18, 1952, and the remainder of the parotid gland including the facial nerve was removed. In addition, several pieces of the masseter muscle were removed for histologic study. Microscopic examination at this time disclosed a few nests of recurrent tumor well within the confines of the remaining salivary tissue (Fig. 3). The sections of the masseter muscle were negative.

It has been gratifying that the disability due to the total facial paralysis has been minimal (Fig. 4). In July, 1953, correction of the facial disfiguration by insertion of fascial transplants was carried out with satisfactory results.

Fig. 4.—Appearance of patient following total removal of parotid gland with the facial nerve. In spite of a total paralysis, the deformity is chiefly in the region of the eyelids. This has subsequently been corrected by insertion of fascial grafts.

COMMENT

The foregoing case of mucoepidermoid tumor of the parotid is presented because of the age of the patient and the relative rarity of the lesion. According to Stewart and co-workers, this tumor comprises only 5 per cent of all salivary gland growths.

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POLYORCHIDISM

A Case Report

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(From the Straub Clinic)

ACCORDING to Lowsley and Porras,[1] true supernumerary testicles are rare although the condition is more often reported, unsupported by microscopic examination. They have justly asserted that many clinical conditions can be mistaken for polyorchidism, which include spermatoceles, small tumors or cysts of the scrotum, hydrocele of the cord, or an omental hernia. Only those cases in which the suspicious extra gonad has been subjected to microscopic identification should be accepted as authentic. According to the authors mentioned, only nineteen such cases have been reported in the literature. The first was by Lane[2] in 1895, and the case to be presented here, we believe, should be added to this small group.

CASE REPORT

S. T., a 19-year-old Japanese man, was examined on Dec. 28, 1953, complaining of a painful swelling in the left groin which had begun about thirty-six hours previously. The onset was gradual, and the discomfort became rather marked prior to noticeable swelling. There had been no nausea, vomiting, or altered bowel movements, and no episodes of a similar nature had occurred previously. His past history revealed that the testicle on the left side had always been quite high and had never been all the way down into the scrotum. No other illnesses or injuries had been encountered. His development had been entirely normal, and there was no history of familial disease.

Examination revealed a Japanese man who appeared to be uncomfortable. He walked in a somewhat crouched position. Temperature was 98.6° F.; pulse was 84; and respirations were 20. He exhibited normal general physical development, possessing all masculine characteristics. Positive physical findings were limited to the left inguinal region, where a partially undescended testicle was present, riding just over the brim of the pubis. The contents of the right half of the scrotum were normal to palpation. The partially undescended left testicle was slightly tender, and on palpation above this point, there appeared to be a firm, movable mass in the vicinity of the internal inguinal ring, or at least in the inguinal canal, which was quite tender, and a cough impulse, though feeble because of the presence of pain, was transmitted to the examining finger.

A presumptive diagnosis of undescended testicle associated with an inguinal hernia complicated by incarceration of bowel or omentum was made, and the patient was admitted to Kuakini Hospital for operation.

Under spinal anesthesia, the usual diagonal incision was made in the left inguinal region which was carried down through Scarpa's fascia and the external oblique fascia in the same plane. The cord with its partially undescended testicle was then mobilized, and the cremasteric muscle was dissected away from the internal ring. A hernia sac was identified and found empty. It was of the funicular type, that is, the distal extremity of the sac was connected by a fibrous band to a complete tunica vaginalis which surrounded the partially undescended testicle. The mass at the internal ring was then obviously something else. The deep epigastric vessels were ligated and, after enlargement of the internal ring, an additional testicle was delivered which was somewhat larger than its lower mate.

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This testicle appeared to be completely normal in every respect except that it possessed no tunica vaginalis and no vas deferens, whereas the lower testicle possessed both with all cord structures. Both testicles had adequate vascular supplies, which united just proximal to the internal ring and appeared to receive blood from common spermatic vessels. At this point, the contents of the right side of the scrotum were re-examined, and the testicle, epididymis, and vas appeared to be quite normal. Since neither of the testicles on the left side could be mobilized sufficiently to transplant to the scrotum, and because of the increased incidence of malignancy in undescended testicles, it was apparent that their excision was the treatment of choice.

Accordingly, the cord and blood supply were amputated as high as possible and transfixed. The hernia sac had been previously dissected free, its neck was closed rather high, and a definitive repair of Hesselbach's triangle, the internal ring, and the inguinal canal was effected without incident.

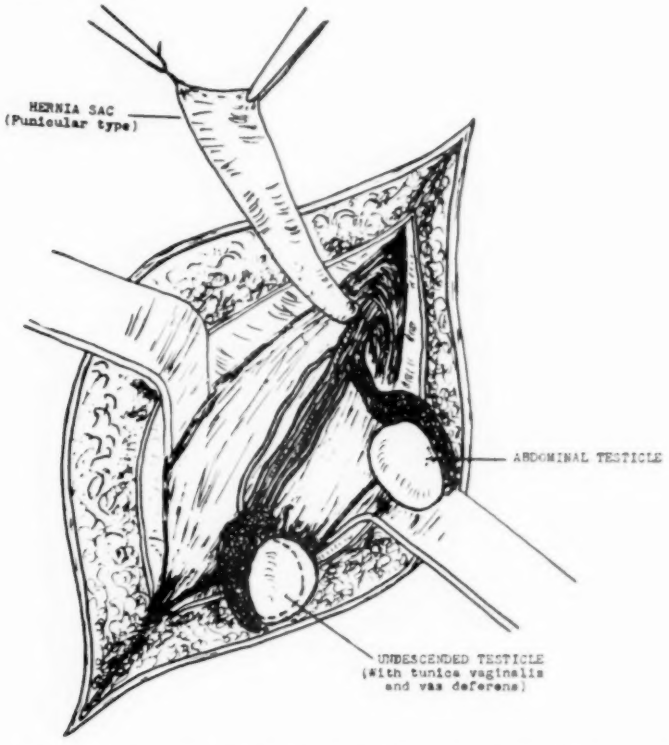

Fig. 1.—Diagram showing exposure of left inguinal canal contents, as encountered in the case described.

The patient's postoperative course was uneventful, and he returned to full duty after a period of one month.

The microscopic pathologic description of the lowermost undescended testicle, which exhibited some atrophy but possessed a full tunica vaginalis and an attached vas deferens, was as follows: Histologic examination showed the microscopic picture of a somewhat atrophic testicle which was made up of relatively few irregular tubules lined by several layers of epithelium. These tubules were larger than normal testicular tubules and in some respects resembled tubules of the epididymis. No evidence of spermatogenesis, however, was observed. The tubules made up a relatively small part of the section, and most of it was composed of dense collagenous connective tissue containing blood vessels which were dilated and engorged with red cells. The small elongated structure noted previously was, indeed, a normal-appearing vas deferens.

The microscopic pathologic description of the higher or abdominal testicle, which possessed no tunica vaginalis and no vas, was as follows: Histologic examination showed

the microscopic picture of a testicle which was fairly normal in its histologic appearance. It was made up of testicular tubules which had a tendency to be somewhat larger than normal and to show considerable desquamation of epithelium. In addition, many of the epithelial cells were vacuolated, having undergone degeneration, and no evidence of spermatogenesis was seen. The tunica albuginea was made up of dense collagenous con-

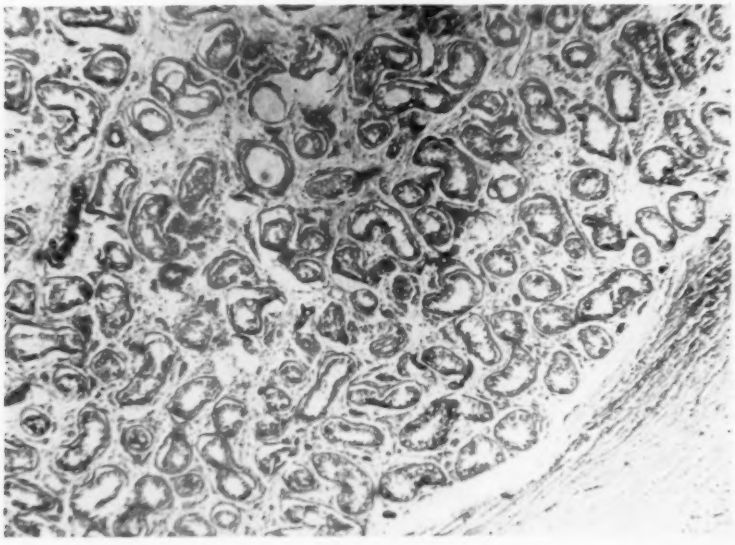

Fig. 2.—Large undescended abdominal testicle made up of atrophic and nonfunctioning seminiferous tubules. Part of tunica is shown in lower right-hand corner. (Hematoxylin and eosin. ×45; reduced ⅓.)

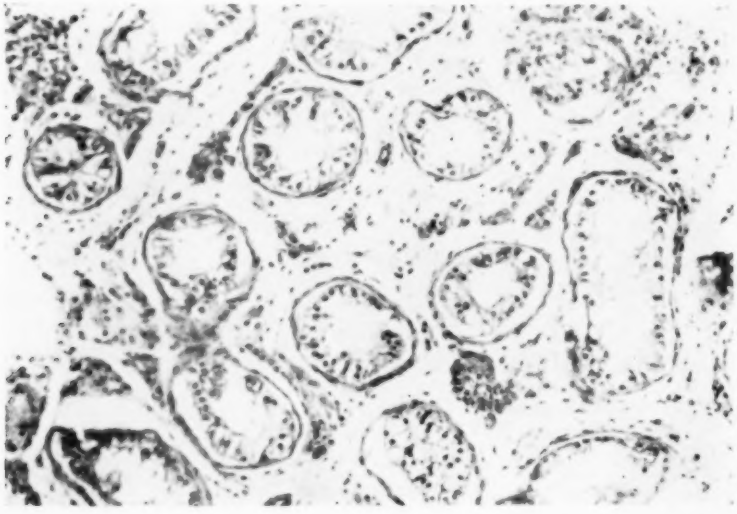

Fig. 3.—Smaller partially descended testicle showing atrophic testicular tubules. Some tubules present in this testicle resembled those making up the epididymis. (Hematoxylin and eosin. ×120; reduced ⅓.)

nective tissue. The second section showed atrophic epididymitis made up of tubules which appeared relatively normal. The third section taken through the elongated mass showed fatty tissue containing many blood vessels and no vas deferens.

This patient was last examined on Feb. 1, 1954. He was asymptomatic, his wounds were healed solid, and there were no alterations in his physical status.

DEVELOPMENTAL ANATOMY

At about the sixth week of embryonic life, the prospective testis begins to develop from the primitive genital ridge, just medial but adjacent to the mesonephros. By condensation of the longitudinal cell mass, the testicle, or ovary, begins to take shape at about eight weeks. The testicle does not develop a tubular system of its own, but appropriates the mesonephric tubules and ducts of the degenerating mesonephros to form its epididymis and vas. At about ten weeks, differentiation of the gonad begins so that testicular and ovarian tissue is separately identifiable. By the third month, the testicle is a well-organized structure and begins its retroperitoneal journey to the scrotum. During the last phase of its descent, it will be remembered that the processus vaginalis picks up a portion of peritoneum as it passes the lowermost peritoneal fold and in turn encloses the testicular side of the organ to form a serous sac, known as the tunica vaginalis. Normally, the remainder of the processus vaginalis becomes obliterated, leaving a fibrous strand as one of the cord contents. Interruption in this course of late events is usually responsible for the formation of various types of indirect inguinal hernias.

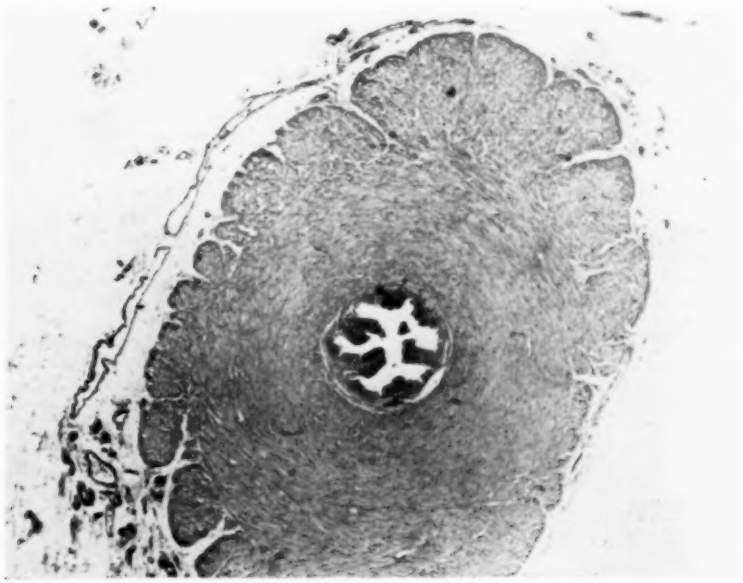

Fig. 4.—Normal vas deferens associated with small, partially descended testicle. (Hematoxylin and eosin. ×45; reduced 1/6.)

DISCUSSION

Since the original genital ridge with its germinal epithelial mass is an elongated structure, it is conceivable that fragmentation during the condensation process could result in the formation of two organs. Further, it is easy to understand the production of an additional epididymis to accompany the supernumerary structure. However, since there is normally only one mesonephric duct, the availability of a vas deferens for each of two testicles on

one side would seem more limited and would require duplication of the mesonephric duct on that side. Since duplication of the vas deferens has been reported as the only abnormality in some instances,[3] such is the probable mechanism. Actually, this concept is consistent with observations made from reported cases of true polyorchidism. Thiessen's[8] case is the only one of the nineteen in which complete duplication of all structures on one side was reported. The usual arrangement in other case reports has been the existence of a single vas to serve two testicles. All variations in the arrangement of a single vas with a single or double epididymis have occurred, in addition to complete absence of all ductal systems.

Of the recorded cases, most were discovered during operations for hernia or exploration for inguinal or scrotal pathologic lesions. Our case exemplifies the usual manner of identification as well as the commonly encountered arrangement: two testicles on one side, with a normal testicle on the opposite; one testicle with its vas deferens and other cord structures, and a supernumerary testicle without vas deferens or cord structures. Obviously the presence or absence of a tunica vaginalis would depend on the degree of descent. Usually both structures on the affected side possess adequate blood supply.

In conclusion, there is one obvious point of emphasis: a supposed third testicle must be differentiated from ectopia, that is, two testicles on one side with an empty opposite scrotal sac.

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HEMANGIOPERICYTOMA OF THE JEJUNUM

A Case Report

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(From the Departments of Surgery and Pathology, College of Medicine, Ohio State University)

HEMANGIOPERICYTOMA is the name given by Murray and Stout[1, 2] to neoplasms arising from cells identified as pericytes by Zimmerman.[3] While reviewing a series of vascular tumors, Murray and Stout[1, 2] observed that nine were composed of these perivascular cells. Subsequently, thirty-two cases have been added by Stout[4] and other investigators.[5-12] Of the tumors reported, only one arose in the small intestine. The case here presented is one of small bowel obstruction due to intussusception caused by a polypoid hemangiopericytoma in the jejunum.

CASE REPORT

N. T. (Hospital No. 5310206A), a 36-year-old white man, was admitted to University Hospital on Dec. 2, 1953, complaining of abdominal pain. Six days before admission the patient developed cramping periumbilical pains accompanied by vomiting of bile-stained material. During the next four days, abdominal distention, constipation, and increasing pain prompted admission to another hospital, where gastric suction was instituted in conjunction with antibiotics and intravenous fluid. Although the patient passed flatus and small amounts of feces, the abdomen became progressively more distended, and the pain assumed a constant character.

Six days after the onset of symptoms the patient was transferred to this hospital. On admission a temperature of 101.6° F., pulse of 110, and respiratory rate of 30 were recorded. The patient was very dehydrated, the abdomen was moderately distended, and no surgical scars or hernias were present. There was generalized tenderness, but no muscle spasm; no masses could be palpated. The abdomen was tympanitic; the bowel sounds were hyperactive without high-pitched rushes. No masses or feces were encountered on rectal examination. The remainder of the physical examination was negative.

Laboratory data included a white blood cell count of 6,300 with 76 per cent neutrophils and 24 per cent lymphocytes. Serum Na^+ was 138 meq., and K^+ 4.5 meq. Roentgenographic examination demonstrated thickened intestinal walls and moderate distention of many loops of small bowel, with fluid levels visible on the upright film. A minimal amount of gas was seen in the colon and rectum; the barium enema studies were normal. A diagnosis of incomplete small bowel obstruction was made.

Gastric suction was started; antibiotics were administered, and the electrolyte balance and the fluid and blood volumes were restored. Twelve hours after admission, when the patient's pulse had slowed to a rate of 82, laparotomy was performed.

On opening of the peritoneal cavity through a mid-abdominal right paramedian incision, several loops of dilated small bowel were encountered. The site of obstruction was found in the lower jejunum, where five inches of intestine had intussuscepted. A firm, rubbery mass was palpated at the advancing margin of the intussusception. By gentle pressure the intussusception was reduced, and the affected segment was found viable, as evidenced by a rapid return of normal color and motility. Through a jejunotomy, a 4 cm. ovoid mass was found protruding into the lumen and attached to the wall by a base 1 cm.

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in diameter. The tumor was carefully inspected and found to arise from the intestinal wall. There was no serosal involvement. The neoplasm including the bowel wall underlying the base of the mass was removed intact; the margins were free of tumor; the bowel was closed transversely with a double layer of interrupted silk sutures. The patient's recovery was uneventful.

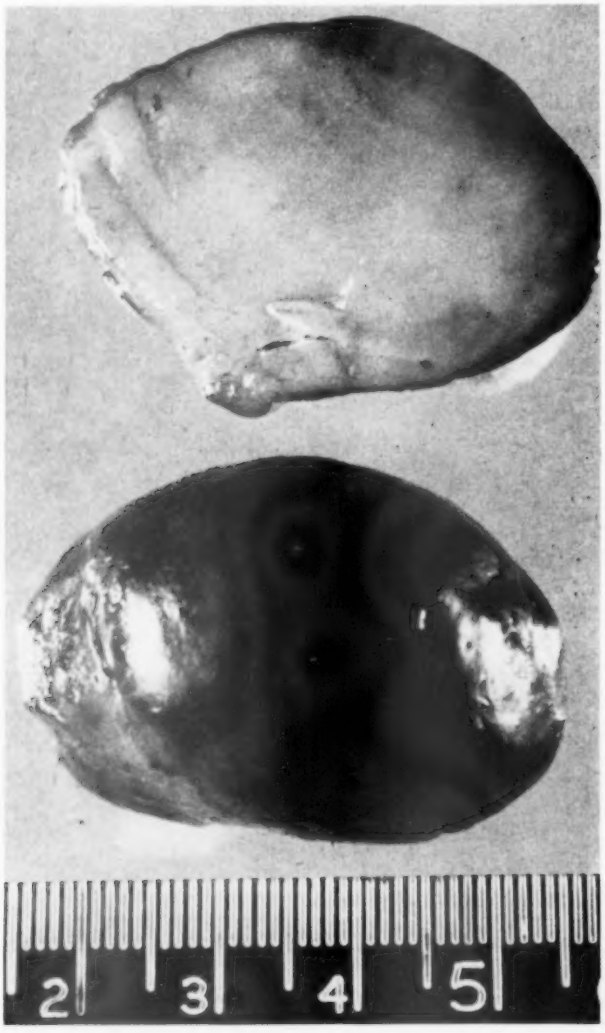

Fig. 1.—Appearance of tumor at time of removal. The superficial hemorrhage is seen on the cut surface.

The specimen was a reddish brown ovoid tumor measuring 4 by 2.5 by 2 cm. It had a smooth surface and was rubbery in consistency. At the base it was encircled by a remnant of mucosa; the tumor had arisen within the intestinal wall and, during its growth into the lumen, had produced focal pressure atrophy and necrosis of the overlying mucosa. The cut surface was homogeneous, glistening, yellow-white, with a peripheral zone of hemorrhage (Fig. 1).

Histologically the tumor was composed of many capillaries and larger vessels with thick collagenous walls surrounded by spindle-shaped and stellate cells (Fig. 2). Reticulin stain disclosed a much larger number of capillaries than was at first apparent; delicate reticulin fibers lay immediately beneath the endothelium (Fig. 3). There was no evidence

of endothelial proliferation. Lying between the capillaries were the spindle-shaped cells noted previously. Many of these were in intimate relation to the subendothelial reticulin, and resembled the pericytes of Zimmerman. These cells had a scanty to moderate amount of cytoplasm and oval nuclei; myofibrils were absent, and mitotic figures were infrequent. There was no histologic evidence of malignancy.

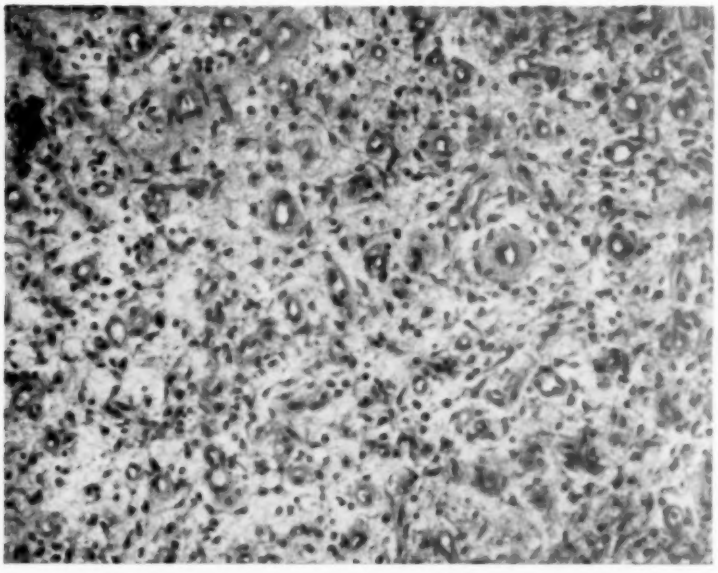

Fig. 2.—Section of tumor showing numerous capillaries surrounded by a connective tissue sheath about which are grouped the neoplastic pericytes. (Hematoxylin and eosin stain. ×150; reduced ¼.)

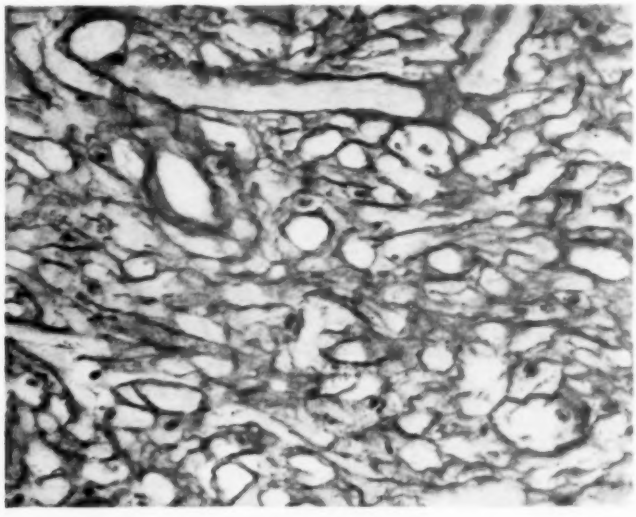

Fig. 3.—Laidlaw silver reticulin impregnation of section demonstrating many occult capillaries. (×450; reduced ⅕.)

DISCUSSION

Most of the forty-one reported hemangiopericytomas were located in the subcutaneous tissue of the extremities. However, several cases have been observed in which the tumor was found in the mesentery or retroperitoneal

space. In only two instances was the tumor located in the gastrointestinal tract. In one of these cases[6] the growth arose in the sigmoid colon and extended into the mesocolon, as well as into the lumen of the bowel. The intraluminal portion was polypoid and superficially ulcerated. Nearly three years after the initial resection, the tumor had recurred and invaded adjacent structures; distant metastases were not found. The second case[5] was of an ulcerating growth that encircled the ileum. The segment bearing the tumor was resected. At autopsy eighteen months later, metastases were found in the liver.

The case presented is the second recorded hemangiopericytoma of the small bowel. The tumor led to an intussusception, which produced symptoms of a jejunal obstruction. The intussusception was due to invagination of the bowel wall by peristaltic action on the polypoid mass. On gross inspection at laparotomy the tumor was thought to be a leiomyoma.

In the differential diagnosis of polypoid tumors of the small intestine, the surgeon should now consider hemangiopericytoma along with leiomyoma, neurilemmoma, and adenoma. The frequency of malignancy in this group of tumors is not yet established because of the small number of cases and the lack of follow-up; however, in approximately 40 per cent of the recorded cases, local recurrence or distant metastasis developed.[12] Resection of the involved segment of small intestine rather than local excision of the tumor would seem to be the treatment of choice.

SUMMARY

A case of hemangiopericytoma producing intussusception and obstruction of the jejunum is reported. A review of the literature disclosed only two other cases of hemangiopericytoma in the gastrointestinal tract. Of these, one was located in the ileum and the other in the sigmoid colon.

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ACUTE OCCLUSION OF THE INTERNAL CAROTID ARTERY

Report of Five Cases

William R. Chambers, M.D., Atlanta, Ga.

ACUTE spontaneous occlusion of the internal carotid artery, masquerading as stroke, multiple sclerosis, and other diseases, is probably much more common than has been generally supposed. Johnson and Walker,[1] in 1951, were able to assemble 107 cases from the literature. Elvidge,[2] using angiography in all suspected cases of vascular injury, found six instances of spontaneous carotid thrombosis in 150 cases, or 4 per cent. Feiring[3] found seven cases in 500 angiograms of patients suspected of intracranial tumor. Sugar[4] stated: "The literature indicates an age variation of from seven to 71 years. Involvement of the left carotid is 6.5 times as great as that of the right." It has also been noted that men are much more often subject to this disease than are women.

The etiology has been described in the literature as arising from an embolus, such as that thrown off by a mural thrombus and by thrombosis of the internal carotid artery. The thrombosis may be retrograde, for example, after ligation of other arteries. It may originate from arteriosclerosis. It has also been described as a manifestation of generalized thromboangiitis obliterans.

The symptoms, according to Sugar,[4] include premonitory headache, vertigo, hemiparesis, hemiparesthesia, and speech defects; temporary blindness is not infrequent. The pupil on the side of the blindness may be transiently miotic. Thrombosis of the central retinal artery leading to atrophy of the optic nerve may occur. Webster, Dolgoff, and Gurdjian[5] described four methods of onset: (1) explosive, simulating stroke; (2) slowly progressive, characterized by remissions and recurrences (which may suggest multiple sclerosis); (3) with visual symptoms; (4) without signs or symptoms. Elvidge[2] described recurring disturbances of a hemiplegic nature, resulting eventually in hemiplegia which is more or less complete. He also spoke of fatigability, headache, blurring of vision, and impairment of memory. Head noises and convulsions have been described by Shapiro and Peyton.[6]

The site of thrombosis or embolism has been most commonly just distal to the bifurcation of the common carotid artery. However, occlusions in or just above the siphon of the carotid artery and in other positions have been described.

As has already been mentioned, the differential diagnosis is at times quite difficult, especially in those cases which have remissions and recurrences of symptoms. Multiple sclerosis is often considered since some of these patients develop nystagmus and interference with speech. The cardinal point is that

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the recurrence can always be referred to pathology in the same locus in the brain, whereas in multiple sclerosis, multiplicity as to location as well as to time is the rule. The original diagnosis in many of these cases has been brain tumor, intracerebral hemorrhage, brain abscess, or subdural hematoma.

Angiography is an essential feature of the diagnosis in these cases. In fact, without it, one can seldom be sure unless an actual operation on the carotid artery is performed and the occlusion is demonstrated under direct vision. However, one must be careful not to make the diagnosis too readily merely on the failure to visualize the dye in the vessel suspected. Aneurysms of the carotid artery as well as other pathologic entities are capable of blocking a portion of the internal carotid system in such a way as to produce a failure to fill. Krayenbühl and Weber[7] observed that a conical narrowing of the dye before it stops is characteristic of thrombosis of the internal carotid. Shapiro and Peyton[6] listed six characteristics of the angiogram suggesting internal carotid occlusion, the first four of which are strong evidence: (1) a conical narrowing of the dye, resulting in visualization of a stump or a short segment of the internal carotid artery; (2) failure to fill the internal carotid artery and a defect in the column of the dye; (3) retrograde flow of the dye into the common carotid artery and on the right side through the innominate to the vertebral artery; (4) irregularities in diameter of the vessel and narrowing of the vessel; (5) failure, on repeated attempts, to produce any filling of the internal carotid; and (6) failure, on repeated attempts, to produce any filling beyond the carotid siphon.

To this, we would like to add an observation of our own. We believe that the diagnosis is most certain when the internal carotid system on the suspected side fails to fill with repeated attempts, while angiography on the good side fills both internal carotid trees across the circle of Willis. Angiography on the unaffected side, however, carries a definite risk of embarrassing the remaining circulation.

Another excellent suggestion as to detection has been offered by Dunning.[8] He suggested that palpation of the artery in the pharynx will demonstrate absence of pulsation of the internal carotid on the affected side.

While some of these patients have appeared to recover spontaneously, as shown in one of our cases, the problem of therapy is still difficult and awaits development. Removal of the thrombosed artery with denervation of the carotid sinus has been suggested; ligation of the external carotid and common carotid artery has also been offered; stellate blocks have been suggested, but many have found them to be of no benefit. Shapiro and Peyton[6] recommended arteriectomy, cervical sympathectomy, and anticoagulant therapy. All workers agree, however, that diagnosis and therapy are of the utmost urgency in these cases since no benefit can be expected unless the treatment is started immediately. Of all the various suggestions, anticoagulant therapy, promptly begun, appears to be the most efficacious.

All our cases were of the acute type, falling into Webster and associates'[5] classification number 1.

CASE 1.—J. S., an 11-year-old boy, was apparently well and in good health until, while walking home from school one afternoon, the right leg suddenly gave way under him. He was found lying in a ditch by a friend who helped him home. He was awake, but unable to speak. Speech returned after approximately thirty to forty minutes, although it was slurred, probably as a result of the appearance of a facial paralysis on the right. He later stated that he had a peculiar feeling in the right arm and leg immediately prior to the onset of the difficulty. The past history was of no assistance.

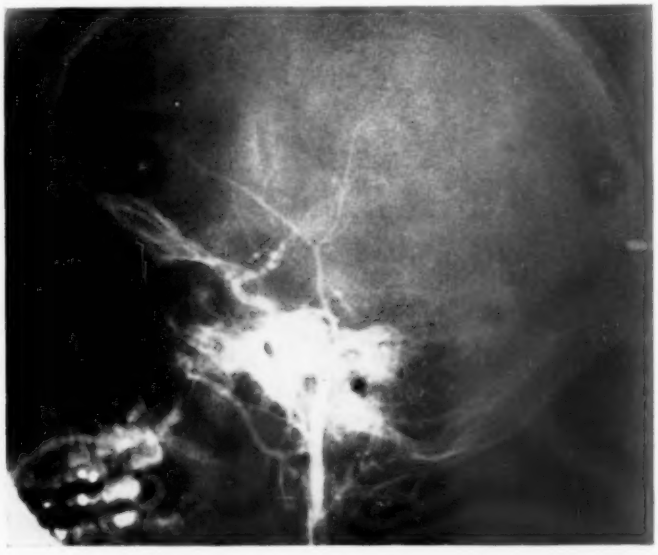

Fig. 1.—Case 1. Occlusion of internal carotid artery as evidenced by conical termination and "beading" at the siphon.

Fig. 2.—Case 2. Complete occlusion of the carotid artery at the base of the skull.

Examination revealed a well-developed and well-nourished 11-year-old child who was almost completely hemiplegic on the right. A positive Babinski reflex was present on the right, as well as an ankle clonus. The abdominal reflexes were absent on the right.

Ophthalmoscopic examination was essentially negative. The pupils reacted to light and accommodation. Extraocular movements were normal. Sensory examination revealed a consistently diminished appreciation of light touch; astereognosis was present in the right hand. Visual fields were unimpaired.

Lumbar puncture showed an initial pressure of 160 mm. of clear, colorless spinal fluid. Angiography revealed conical narrowing of the internal carotid artery just beyond the siphon, with a series of beadlike shadows just distal to this point, as shown in Fig. 1.

Anticoagulant therapy was started immediately, and physiotherapy was undertaken. At the end of six months, he was walking quite well and his gait was improving all the time. The right upper extremity had increased fairly well in strength and coordination, although maximal return had not yet been achieved. It was felt that, with further treatment, he might regain almost normal motor activity.

L. Fig. 3. *R.* *R.* Fig. 4. *L.*

Figs. 3 and 4.—Case 3. Occlusion of the internal carotid artery as evidenced by filling of both internal carotids from injection on the healthy side, while no filling was possible on the diseased side. (Fig. 4 should be reversed.)

CASE 2.—J. H. was a 38-year-old white man who had a sudden onset of right hemiplegia. Angiography was performed on two separate occasions by the open method, and a complete occlusion of the internal carotid was demonstrated at the base of the skull, as shown in Fig. 2.

This patient was not subjected to anticoagulant therapy since the condition had come to the attention of the neurosurgeon rather late. Eight months later, the patient was somewhat improved in that he was able to walk with the use of a cane, but the right arm was still completely useless and speech had not improved.

CASE 3.—E. C., a 48-year-old white woman, while at work, noticed without previous warning the onset of some weakness on the right side. It was necessary for her to sit down in a chair in order to continue. In a few hours she was completely aphasic, hemiplegic on the right, and had to be taken home. She progressed rather rapidly to an almost complete amentia. Air studies were made and showed some atrophy of the cortex. A diagnosis of Alzheimer's disease was made. After five weeks, when there was no improvement, she was brought to us and a carotid angiogram made bilaterally showed filling of both sets of cerebral arteries from the unaffected side. On repeated attempts, however, injection of the common carotid on the affected side showed filling only of the external carotid. This is a good illustration of the importance of carotid angiography in this disease and an example of one method of proving the diagnosis.

CASE 4.—E. M. was a 44-year-old white man who had been in excellent health until one Sunday when he was driving home from church. His wife, who had not accompanied him, was watching him approach in his automobile when she noticed that the automobile was swerving badly. He was evidently able to run the automobile against the curb and stop. By the time she reached him, he was completely paralyzed on the right side and was aphasic.

Examination showed a well-developed man of 44 years in acute distress with a slightly irregular pulse and a somewhat dusky, cyanotic appearance in spite of oxygen. He was completely paralyzed on the right side and profoundly aphasic. Electrocardiogram showed no definite evidence of heart disease. He had evidently aspirated, and bronchoscopic examination was undertaken with the removal of mucus plugs from the right bronchus. A carotid angiogram was carried out and showed exactly the same findings as were seen in Case 3. For this reason illustrations are not shown. In spite of therapy, probably because of profuse aspiration before the patient was seen, fulminating pneumonia developed and the patient died.

CASE 5.—H. M. was a 45-year-old white woman who, for three weeks, had been having an early morning headache which was severe enough to wake her and which had become progressively worse. The headache was accentuated by flexing the neck forward and by rotating it too far, as though she had a crick in the neck. Two months before examination, she was taking her afternoon nap when the headache awakened her and was almost unbearable. She then suddenly developed an inability to talk and could not move the right arm or leg. This lasted for about one hour and then the motor power returned. There were residuals, however, of numbness and awkwardness in the right hand. There were paresthesias about the right side of the face, especially involving the angle of the mouth. The speech disturbance lasted about fifteen minutes and then disappeared. The headache continued for about two weeks after this episode. The past history, except for a mild diabetes, was essentially negative.

Examination revealed a woman 45 years of age who was intelligent and cooperative and who showed no signs of intellectual deficit. Speech appeared to be normal. There were a slight nystagmus which was present on gaze to either side and minimal pyramidal tract signs on the right. Babinski and Hoffmann signs were not present. There was a slight relative astereognosis of the right hand. Angiography was undertaken, and filling of the left internal carotid artery could not be obtained. Regurgitation backward into the external carotid artery was present. Since this was felt to be inconclusive, angiography was undertaken by the open method. The internal carotid artery consisted of a firm, fibrous band without evidence of pulsation. The cervical sympathetic chain was therefore resected. The patient had no further trouble except for an occasional headache.

SUMMARY

Acute occlusion of the internal carotid artery is capable of simulating many other diseases. Carotid angiography, critically interpreted, and direct exposure of the vessel by surgery, and direct palpation of the artery in the

pharynx, are the only means by which one may reach a final diagnosis. The condition is probably far more common than is generally thought. Immediate recognition and application of anticoagulant therapy appear to offer the best hope for recovery.

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BOECK'S SARCOID OF THE PERITONEAL CAVITY

A Case Report

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THE disease known as sarcoidosis has been described by many investigators and given different names since 1869. It was apparently first described in that year by Jonathan Hutchinson, who reported a patient with peculiar purplish, raised lesions on the legs, fingers, and forearms. In 1889, Besnier gave a more complete description of a patient with swellings of the nose, ears, and interphalangeal joints of the fingers. In 1899, Boeck gave us the first complete clinical and miscroscopic description of a disease manifesting multiple skin nodules which resembled the round cells of sarcoma. He called it "multiple benign sarcoid of the skin." Subsequently, he reported several more cases which involved lymph nodes, mucous membranes, bones, and internal organs. He concluded that it was an infectious process, nearly related to tuberculosis, and possibly due to the tubercle bacillus.

It has been called by a variety of names, such as: "lupus pernio" (Besnier); "benign lympho-granulomatosis" (Schaumann); "osteitis tuberculosa multiplex cystica" (Jüngling); "maladie de Besnier-Boeck"; and "Hutchinson-Boeck's disease."[5]

It can be described briefly as a benign generalized disease of the reticuloendothelial tissue, presenting the symptoms of a chronic infectious granuloma. It may involve any organ of the body, but has a predilection for the lymph nodes, particularly in the chest. It has a tendency to relapse and at times heals spontaneously. It gives rise to only moderate constitutional reactions. It has often been described in the eye and the parotid gland. It has a tendency to cause a peculiar cystic degeneration of the bones of the fingers.

The exact etiology is unknown, but many men believe it is related to tuberculosis, possibly the bovine type. It certainly resembles it grossly and microscopically, except no one has consistently demonstrated actual tubercle bacilli in the lesions. It resembles Hodgkin's disease and is often mistaken for it. The consensus of opinion seems to be that it is a virus infection causing a chronic granuloma similar in some respects to lymphogranuloma inguinale.

The characteristic pathologic features are similar to those of miliary tuberculosis and tend to involve lymph nodes, lung, liver, spleen, bone marrow, and skin. Wherever it is found, the histologic appearance is essentially the same. The lesions appear in collections of large epithelioid cells arranged in the form of miliary tubercles. These collections of cells may attain large proportions and appear as tumorlike growths. They do not tend to caseate, as does true tuberculosis, and there is even an absence of inflammatory reaction

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around them. Occasionally a large type of giant cell is seen in the lesion. There is a tendency to fibrous degeneration throughout the "tubercle."

The tuberculin reaction was found to be positive in about 40 per cent of the cases reported by Kissmeyer[6] in 1932. He concluded that the incidence of positive tuberculin reactions was approximately that which one would expect in any group of patients who did not have clinical tuberculosis. Longcope[8] found only four positive reactions in twenty-six cases tested. The value of this test is quite equivocal.

The disease has a predilection for young adults. In Kissmeyer's[6] series of 200 patients, one-half of them developed the disease before the age of 30. The sexes were affected almost equally. It may occur in both Negro and white individuals. It is apparently more common in the Scandinavian countries, from whence Boeck made his contribution (Norway). However, Longcope[8] reported thirty-one cases in 1941, in which seven patients were white and twenty-three were Negro.

The literature is full of reports of Boeck's sarcoidosis. Most of them are cases involving the skin, lymph nodes, chest, bones, or eyes. The liver and spleen are not infrequently mentioned. Less often can be found reports of the disease affecting nearly every other organ and tissue in the body. We are encouraged to report our case, however, because a careful search of the literature failed to reveal another similar instance where the lesions of sarcoidosis predominately involved the peritoneal surface. The most closely related case which we could find is one reported by Montamus[11] in 1938. His patient developed a tumorlike mass in an old McBurney scar, and upon excising it, several small nodules were discovered on the inside surface of the peritoneum.

CASE REPORT

This patient was a 37-year-old Mexican woman, who entered the hospital Feb. 24, 1953. Her chief complaint was a "lump" in an old gall bladder scar which she had noticed three weeks previously. She had a slight pain and a burning sensation in the mass, especially if she strained or lifted heavy objects. She felt fairly good otherwise, and had no cough and no pain elsewhere in her body. She had lost about 15 pounds in the previous three months, however.

Her past medical history revealed the fact that she had had five normal pregnancies, with four children living and well. One child had died in infancy, cause unknown. In 1946, she had had a right salpingo-oophorectomy for a chronic pelvic inflammation disease. In 1948, she had had a cholecystectomy for gallstones and chronic cholecystitis.

The family history revealed the fact that her father had died in 1920 of pneumonia. Her mother was living and well. She had five brothers and sisters living and well. There was no history of tuberculosis, diabetes, or carcinoma in the family.

Physical Examination.—She was a slightly undernourished Mexican woman, who did not appear acutely ill and was not suffering pain. Blood pressure was 118/70, pulse was 74, respirations 18, and temperature 99° F.

The head and neck were essentially negative. There were no enlarged lymph nodes in the neck.

The upper extremities were symmetrical and well developed. No swelling or deformity of the fingers or hands was noted.

The heart, lungs, and thoracic wall were essentially negative.

The abdomen was soft and relaxed. There was a hard, fixed, elliptical mass just beneath the lower half of an old gall bladder incision in the right upper quadrant. It measured approximately 10 by 5 cm. and was somewhat tender. It did not bulge on coughing. It was fixed to the deep structures of the abdominal wall, but apparently not attached to underlying organs. The skin and scar were only slightly attached to this underlying mass, which had a rather nodular feel.

The pelvic examination was essentially normal, except for a slight cystocele and rectocele.

The back and lower extremities were essentially normal.

Laboratory Studies.—The urinalysis was entirely negative. Blood count was: hemoglobin 97 per cent; red cells 4,450,000; white cells 5,000, of which 44 per cent were neutrophils, 46 per cent were lymphocytes, 3 per cent were eosinophils, 2 per cent basophils, and 5 per cent monocytes. The blood sugar was 100 and the nonprotein nitrogen 37. The Wassermann and Kline tests were negative.

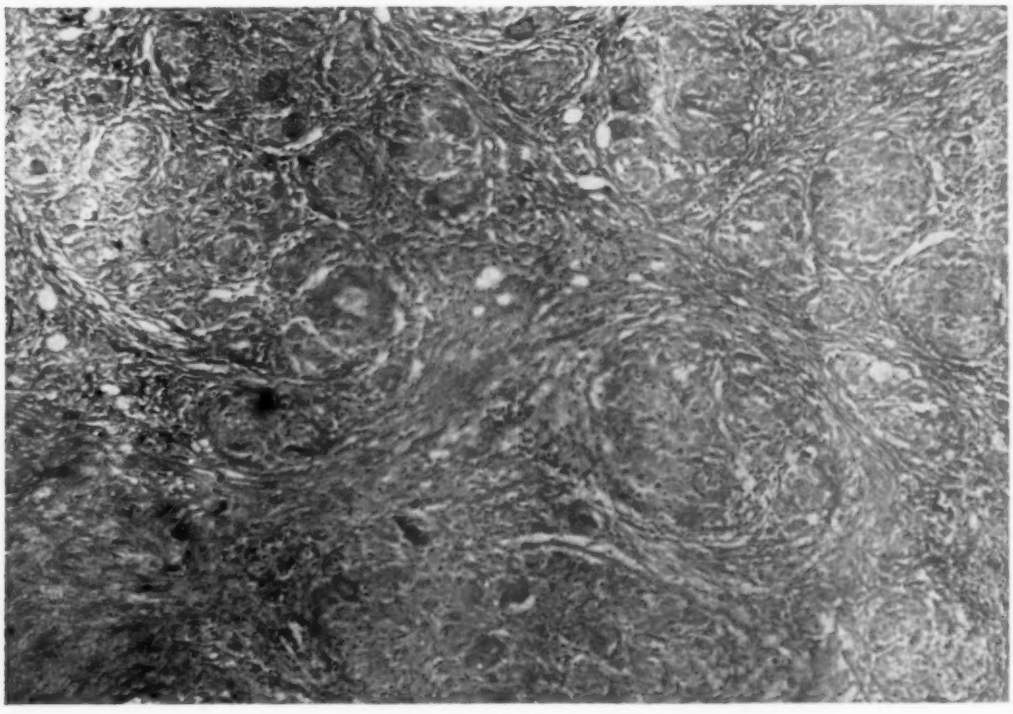

Fig. 1.—Low-power view of the specimen showing the circumscribed groups of epithelioid cells, with several multinucleated giant cells. Note that there is no caseation present, although there is a "tubercle-like" formation.

An x-ray picture of the chest revealed no masses in the mediastinum or lung fields. Nothing abnormal was reported in the film.

Presumptive diagnoses were made of either incarcerated omental hernia or desmoid tumor of the abdominal wall.

Operation.—An elliptical incision was made over the tumor mass, including the old scar. The dissection was carried down through all layers of the abdominal wall. Peculiar whitish, glistening nodules were encountered, diffusely infiltrating in all directions. Some of them were quite small, but others were larger and had coalesced to form a matted tumorlike formation just below the old incision. The incision was carried down to the peritoneum, which was opened rather widely. Upon introducing the hand in the peritoneal cavity, it was discovered that the entire peritoneum was studded with innumerable tiny nodules of the same character as the larger nodules in the abdominal wall. The abdominal organs were inspected, and these

nodules were found on the loops of intestines, the surface of the liver, and the pelvic organs. The large mass in the layers of the abdominal wall was excised as completely as possible, so that closure could still be effected. However, many of the nodules in the fascia were left unavoidably. The abdomen was closed in layers without drainage. Tension sutures were used in addition to the usual technique.

The pathologic report of the tissue removed was as follows: The specimen consisted of a very irregular portion of tissue taken from the abdominal wall. Grossly multiple nodules could be felt. These nodules were very irregular, the largest measuring roughly 1.5 cm. in diameter, and were matted together. Microscopic studies: Multiple sections of tissue submitted showed fat and connective tissue in which there were a large number of circumscribed lesions. These showed some lymphocytic reaction around them, although it was not marked in most areas. The lesions showed rather typical epithelioid cells, and in many of them, multinucleated giant cells were present. The lesions resembled tubercles; however, caseation necrosis was not seen in any of them. No acid-fast organisms were seen on the slides stained for tubercle bacilli. This did not definitely rule out tuberculosis, but in the phase of no caseation and not finding tubercle bacilli, the diagnosis of sarcoidosis had to be considered.

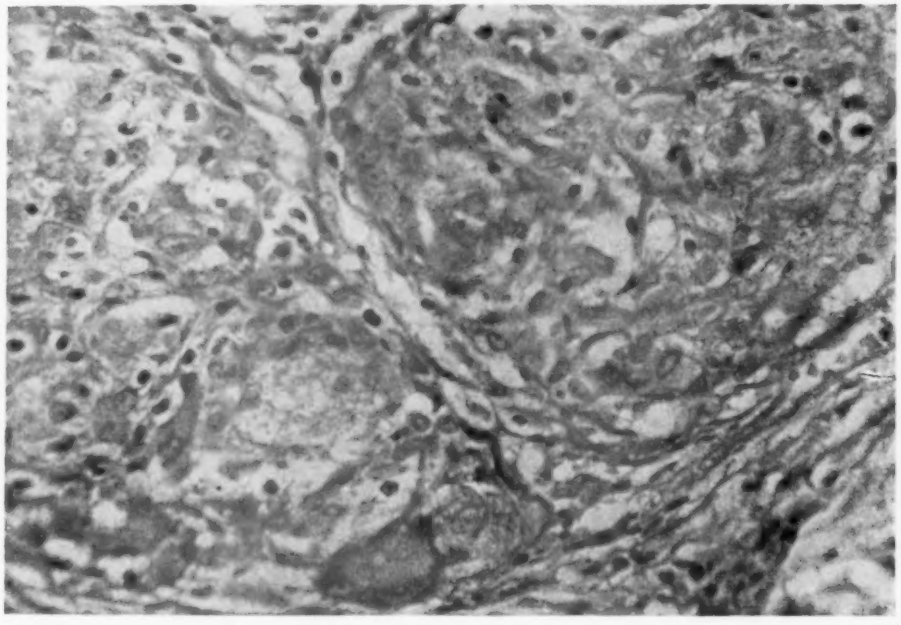

Fig. 2.—High-power view of the lesion in Fig. 1.

The patient made an uneventful recovery from the operation and left the hospital on the tenth postoperative day. While she was in the hospital, an x-ray picture was made of her hands, which showed a normal bone structure and no evidence of cystic changes in the phalanges. A tuberculin patch test was made, which was positive.

Because of recent favorable reports in the literature of the use of cortisone in treating Boeck's sarcoid (chiefly in the eyes), it was decided to try it on this patient. She was given 100 mg. of cortisone each day for about six weeks. The induration around the incision softened and disappeared. She was seen from time to time, and no evidence of recurrence was found. She gained 15 pounds in weight and had no symptoms referable to the abdomen. When last seen Jan. 15, 1954, the abdomen was entirely soft and pliable, and no masses or areas of induration were present. The pelvis was negative by vaginal examination. We think that there is no sarcoidosis remaining in the abdominal wall or the peritoneal cavity at this time.

COMMENT

Boeck's sarcoid is evidently a chronic granuloma which may present a picture not unlike that of miliary tuberculosis. It has been known to affect nearly every organ and tissue in the body. Most of the cases reported in the literature have been those involving the skin, lungs, lymph nodes, eyes, liver, or spleen. It has a tendency to regress and is relatively benign. Death occurs from complications and sequellae rather than from the disease itself. However, it usually runs a course of several years.

Freiman[4] has written extensively on the subject and has described cases involving the lungs, heart, kidney, liver, stomach, and intestines. However, he did not mention the peritoneum. Kulwin and associates[7] in 1949 reported two cases in the gastrointestinal tract. Appell and Pritzer[1] described a case of pyloric obstruction due to sarcoid of the stomach. Phillips and Luchette[13] reported a rare case of rupture of the spleen due to sarcoidosis. Dagradi and co-workers[2] reported an interesting case of marked hepatosplenomegaly with jaundice. Oppenheim and Pollack[12] reported forty-two cases, chiefly in the lung, skin, lymph nodes, and submaxillary gland. They mentioned one case in the stomach, but none in the peritoneum.

Treatment of this disease with cortisone and ACTH has been tried in the past three years. Heathfield[3] reported a case of sarcoidosis involving the lymphatic system, liver, and eyes which showed striking improvement following the use of cortisone. Sones and associates[17] reported improvement in two advanced cases of the disease using the drug. Miller and Bass[10] used both ACTH and cortisone and concluded that cortisone was superior. Siltzbach[15] studied thirteen cases of patients treated with cortisone and noted improvement of varying degree in all patients. Posner[14] reported a case of severe bilateral uveitis and enlargement of mediastinal nodes, which cleared up with cortisone in one month. Small[16] reported two cases of pulmonary involvement which improved dramatically within a few days.

SUMMARY

Sarcoidosis has been known as Besnier-Boeck-Schaumann[5] disease.

It is a benign lymphogranulomatosis, producing lesions similar to those in tuberculosis.

It may affect most of the organs and tissues of the body. Most of the cases reported are those involving the skin, lungs, lymph nodes, eyes, and bones. Occasional reports in heart, liver, spleen, and intestines are seen.

It runs a chronic course, often for years, but occasionally spontaneously regresses.

This case is the only one with extensive peritoneal involvement which we could find in the literature.

We believe that the prompt and complete clinical relief can be attributed in great measure to the use of cortisone in this case.

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INTRAHEPATIC CHOLANGIOJEJUNOSTOMY

A Short Review With a Case Presentation

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INTRODUCTION

THIS procedure, which is an anastomosis of one of the intrahepatic bile ducts to the jejunum following a partial resection of the left lobe of the liver, was devised and described by Longmire in 1948.[1] Since then, twenty-three cases have been reported in the literature, six operations having been performed for malignant and seventeen for benign extrahepatic bile duct obstructions.

INDICATIONS

Indication for the procedure is complete obstruction with destruction of the extrahepatic ducts where other more popular or standard procedures are either technically too difficult or would make the operative time too long, thus jeopardizing the life of a patient immediately or subsequently because of the extra burden added to an already markedly damaged liver.

CAUSES OF OBSTRUCTION

Strictures, most of which are due to operative trauma[2, 3] at the time of cholecystectomy or other right upper abdominal surgery, have increased in frequency. The trauma responsible for these strictures may be due either to crushing, excision, incision, ligation, especially when transfixion sutures are used, or perforation of the bile ducts. Localized or extensive strictures may thus result, it being believed that the extensive fibrosis with complete occlusion follows the bathing of the exposed extrahepatic ducts in a pool of irritating bile in the infrahepatic region when external drainage is inadequate. Calculi, neoplasms, benign or malignant, of the pancreas, ampulla, or the ducts, inflammatory conditions, especially of the pancreas, and congenital anomalies account for most of the other causes.

METHODS OF REPAIR OF STRICTURES

End-to-End Anastomosis.—This is accomplished by finding and mobilizing both the proximal and distal ends of the ducts, which in certain cases might be extremely difficult, anastomosing mucosa to mucosa, and splinting and decompressing the duct with a T tube either distal or proximal to the anastomosis. Lahey[3] reported best results with this type of a repair and strongly recommended it because of the preservation of the sphincter of Oddi. One important factor in this repair is leaving the T tube in long enough so

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that no contracture of the anastomosis develops. The time recommended by Lahey[3] is at least one year. The other factor, which also applies to other types of repair, is the excision of all the scar tissue from the ends of the ducts so that normal mucosa may be anastomosed to normal mucosa, thus minimizing the formation of scar tissue.

Anastomosis of the Proximal Duct or Ducts to the Duodenum or Jejunum.—Walters[4] reported best results when the common duct was anastomosed to the duodenum, and he has also shown that cholangitis is due to recurrent stricture with biliary obstruction rather than to reflux of duodenal contents into the biliary tree.

Cole[2] prefers anastomosis of the proximal duct to a Roux Y arm of jejunum, with which he has obtained best results, rather than jejunal loop anastomosis, which occasionally is responsible for cholangitis due to regurgitation. He also has stopped utilizing splints for the anastomosis, for his end results have been better in cases where no splints were used.

Intrahepatic Cholangiojejunostomy.—This method should be added to the surgeon's armamentarium for it is a very expedient method in a poor-risk patient where the dissection at the hilus of the liver would be long and tedious because of adhesions, marked scarring, loss of landmarks, and troublesome bleeding.

In cases of long-standing obstruction, the liver function may be and usually is markedly decreased because of biliary cirrhosis. Portal hypertension with esophageal varices may be present. But because of the obstruction, different degrees of liver enlargement will occur, and with long-standing obstruction the liver is usually very large unless the condition is almost terminal, in which case the liver starts to shrink in size. Considering the fact that the liver is large and the intrahepatic bile ducts are dilated and thickened and the Glisson's capsule is thickened, the operative procedure which has been adequately described by Longmire[1, 5, 6] becomes not too unusually difficult.

CASE REPORT WITH A THIRTEEN-MONTH FOLLOW-UP

Mrs. E. A., a white woman aged 44, was admitted to the Allentown Hospital on March 13, 1953, for the investigation and treatment of recurrent jaundice. On Jan. 24, 1950, a cholecystectomy for chronic calculous cholecystitis was performed on her at a private hospital (unfortunately the record of the operative findings and the procedure carried out could not be obtained). She had had a drain (not a T tube), and she stated that she started draining greenish yellow bile immediately after the operation and kept on draining until March 25, when the drainage stopped spontaneously. She felt well until July, 1950, when she became jaundiced, the urine became dark brown, and the stool acholic. After about three weeks the jaundice cleared up, but it recurred again in November, 1950, and this time was accompanied by anorexia, pruritus, weakness, and tiredness. She had nine such episodes. With similar symptoms she presented herself to the hospital.

Physical examination revealed a relatively well-nourished woman weighing 124 pounds, having bronze-colored weather-beaten-like skin, and whose apparent age was greater than her chronological age. The temperature was 99.6° F., pulse 80, and respirations 18. The sclera were markedly icteric. The head, neck, chest, and heart were normal.

The abdominal examination revealed a markedly enlarged liver, the anterior edge, which was sharp and uneven, being a handbreadth below the costal margin. The spleen was not palpable. A diagnosis of stricture of the common duct with biliary cirrhosis and mild hepatocholangitis was made. The laboratory reports made were white blood count, 10,600; polymorphs, 70; lymphocytes, 26; monocytes, 2; basophils, 2; coagulation time, three minutes; icterus index, 40.2; serum protein, 5.2 Gm.; albumin-globulin ratio, 1.7/1; serum bilirubin, 4 plus (immediate direct); alkaline phosphatase, 9.1 units; prothrombin time, 16.5 seconds (85 per cent concentration), control, 15.5 seconds; blood urea nitrogen, 9.5 mg.; urine was positive for bile; stool was acholic.

Fig. 1.—Postoperative cholangiogram.

She was placed on a high-protein, high-vitamin, including vitamin K, low-fat diet and was given 4 pints of blood. On March 18, 1953, she was operated upon under continuous spinal anesthesia. Dense fibrotic adhesions between the stomach, duodenum, hepatic flexure, omentum, and the liver bed were encountered on entrance of the upper abdomen. These were carefully dissected off and the hepatoduodenal ligament was identified. A knob of fibrous tissue measuring approximately 1.5 cm. in diameter was found at the mid-lateral portion of the hepatoduodenal ligament. After this was dissected free, the distal end of the common duct was found attached to it. Further dissection was carried out proximally, and the portal vein and hepatic artery were dissected free up to the hilus. There was no sign of the proximal common or hepatic ducts except for a narrow,

fibrotic, tubular-like atresic structure which disappeared in the hilum of the liver. By this time the operating time was approximately three hours, so a decision was made to put drains in the Morison's pouch and mark the distal duct with the idea of reoperating within several days. Postoperatively the patient did relatively well; on the third postoperative day some bile started draining through the cigarette drains. This drainage increased for the next three days and then decreased, so that by March 30, 1953, the drainage had practically stopped again. The blood picture was good because of the transfusions, so on April 1, 1953, she was reoperated upon. Much to the surgeon's chagrin, the adhesions were surprisingly dense about the hilus of the liver again. When these were separated, oozing was so marked that it was hopeless to try and proceed with further dissection. A decision was then made to perform an intrahepatic cholangiojejunostomy. The procedure carried out was slightly different from that described by Longmire. The triangular ligament did not have to be cut because of the marked enlargement of the liver; the liver, literally speaking, was "bursting at the seams." Mattress sutures were placed in the anterior inferior edge, and, immediately after the first needle puncture, white bile just kept pouring out. When the liver was cut into for approximately two and one-fourth inches, a duct measuring about 1 cm. in diameter was encountered. A wedge-shaped piece of liver was removed, the duct was mobilized for about 1 cm., then the jejunum was severed about twelve inches distal to the ligament of Treitz, and an end-to-end, mucosa-to-mucosa anastomosis of the intrahepatic duct to a Roux Y arm of the jejunum was performed using interrupted 0000 silk sutures. The anastomosis was made around a long-arm No. 18 Fr. T tube which was inserted into the jejunum about three inches away from the open end with one arm threaded through the open end into the bile duct and the other arm threaded distally into the jejunum. The long arm of the T tube was brought out through a stab wound in the left anterior abdominal wall after purse-string sutures were placed in the jejunum around the tube. The end-to-side enteroenterostomy was next completed, the raw liver area was covered with Gelfoam, cigarette drains were placed into the upper abdomen, and the abdominal incision was closed. The patient's temperature rose to 103° F. after the operation which was due to a blood transfusion reaction, but after that she made a very uneventful recovery, the temperature ranging from 99° to 101° F. the first five days, then gradually coming to normal within ten days or so. The stool became colored within six days. Bile drained well through the T tube. The cigarette drains, which drained a slight amount of bile-stained serosanguineous fluid, were removed by the eighth postoperative day. On April 23, a cholangiogram was taken by the instillation of a contrast material through the T tube, with the patient placed in a Trendelenburg position. Good communication between the right and left hepatic radicals was seen to be present through a remnant of the common hepatic duct (Fig. 1).

The patient was discharged on the following day. The pathologic report on the liver was chronic hepatitis.

Six months postoperatively the T tube was removed, and the opening closed spontaneously within twenty-four hours. On January 23, nine months after discharge, the patient weighed 133 pounds. She generally looked well. The color of the skin appeared normal. She ate everything and had no chills. The liver was no longer palpable. The serum bilirubin was 0.15 mg. (direct) and 2.2 mg. (indirect); icterus index, 10.2; total protein, 6.8 Gm.; cephalin flocculation, forty-eight hours, 2 plus.

She was again seen in June, 1954, and she feels perfectly well.

SUMMARY

A short review of biliary stricture is presented along with another case report of a successful intrahepatic cholangiojejunostomy performed upon a patient upon whom a different procedure would have been extremely hazardous, if not unsuccessful. The use of a long-arm T tube not only gave the

anastomotic line a chance to heal without stenosis but also gave the operators an opportunity for a roentgenologic follow-up with visualization of the hepatic radicals.

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Editorials

The Influence of the Korean Conflict on Residency Training in Surgery

THE years 1951 and 1952 offered an unusual test of the American residency program in surgery. During these years most of the emergency, traumatic surgery done in the American hospitals in Korea was performed by young medical officers who had completed only one to three years of a surgical residency. The Army in Korea in 1951 did not have the support of an adequate number of well-trained surgeons. The inexperienced surgeons, partially trained, were therefore placed in positions designed for mature surgeons. They were given great clinical responsibilities.

As in wars and other conflicts, many of the principles of military surgery had to be relearned. The civilian residencies, in general, had not adequately taught the principles of the surgery of trauma. Thus, as the principles were relearned, unnecessary mistakes were often repeated. The surgeons were, however, alert, interested, and conscientious. They developed rapidly and turned in an excellent performance in the care of the casualties.

As the techniques of arterial repair became applicable to the battle casualty, it became apparent that most of the young surgeons required additional technical training. This deficiency in training resulted in the loss of some limbs until the technique was learned.

Many of the surgeons of the Regular Army had not had special training in the emergency surgery of trauma. Their residency training had closely paralleled that of civilian hospitals. Surgery in a combat army is not civilian surgery in tents. There are many problems peculiar to work in the field and to the handling of mass casualties. Furthermore, everything possible must be done to reduce the mortality of battle casualties and to prevent needless deformities. We cannot constantly relearn lessons previously proved to be of value in therapy. These mistakes must be prevented by a coordinated effort in civilian and military training programs.

Four recommendations might help prevent some of these mistakes in the future.

1. The medical services of the armed forces should extend the Medical Education for National Defense program in our medical schools and should point out the great importance of special training in trauma during residency training.

2. The surgeons responsible for the training of younger men in civilian hospitals should instill in their students the ideal that no higher honor can come to an American physician than that of serving the combat casualty. Medical educators must recognize and teach that the medical services are essential to the over-all welfare of the American people. Their mission can-

not at all times be carried out by the regular corps. At such times, it is the privilege of every physician to offer his service. The infantryman is drafted and placed in the front lines by indirect order of the American people. His injury, deformity, or death is not of his own choosing but in defense of, and by order of, the American people. To serve this man is an honor. It is, therefore, with a sense of pride and in an entirely constructive spirit that the physician enters military service. It is time for American medicine to reemphasize this moral code.

3. In support of this moral code, surgical teachers in civilian schools and hospitals should teach the principles of the surgery of trauma. To the general field of traumatic surgery must be added the principles of arterial surgery, and the advantages and limitations of the plasma volume expanders.

4. The surgeons of the regular services should accept their primary responsibility, trauma, and make it a part of the foundation of their residency training programs. The medical services of the armed forces have an opportunity to study trauma that cannot be duplicated by any other organization. Just as the staff of a tuberculosis hospital studies tuberculosis, or a cancer hospital studies cancer, the medical services must intensively study trauma. No other institution has an opportunity or responsibility in the field of trauma comparable to that of the armed forces. To fail to recognize and to develop this opportunity is first to neglect the wounded soldier and second to retard the development of the medical service of the armed forces.

The implementation of these recommendations would do much to overcome the problems encountered in Korea as well as those that may be encountered in the future.

The young, incompletely trained surgeon was placed in an unfair professional position by the shortage of available, well-trained surgeons. He did an excellent job and developed as a surgeon and as a man. The problems he faced, however, must not each time be faced anew. Surgeons in both civilian and military institutions must adjust their residency training programs to provide additional protection to the American people in the field of trauma.

—John M. Howard

Colles' Fractures

THIS is one of the most frequent of all fractures and is usually regarded as a relatively mild injury in which the displacement of the fragments can be corrected with comparative ease and a fracture in which union practically always occurs within a reasonably short time. Consequently, in fracture clinics the treatment is often entrusted to a neophyte and in private practice is undertaken with confidence by the general practitioner.

Yet those surgeons who have had a wide experience in the treatment of fractures know that the lesions included under the term Colles' fracture may vary from a simply transverse fracture of the distal fourth of the radius with

practically no displacement to one in which the distal portion of the bone is not only broken across, supinated and displaced upward and backward, and hyperextended on the shaft, but is extensively comminuted and the cancellous bone so compressed that the effect is that of a loss of substance in this area. Furthermore, the fragments may be firmly impacted in the abnormal position. In a fracture of the latter type it may be almost impossible to obtain a result which will be satisfactory to the surgeon and to the patient. By this I mean a wrist and hand which are practically normal in function and in appearance.

The unsatisfactory results are due to deformity, pain, weakness, and stiffness of the hand. The deformity may be a shortening of the radius with radial deviation or displacement, hyperextension of the distal fragment, supination of the distal fragment, posterior displacement, or broadening of the distal fragment or various combinations of these. The limitation of motion at the wrist and pain are due to disorganization of the radiocarpal and distal radio-ulnar joints. The weakness may be due to deformity or pain or both. The stiffness of the hand is due to fibrosis, and this seems to be a direct result of persistent swelling. However, there is also a constitutional factor, as some individuals are particularly prone to develop stiffness of the hand after such injury.

So frequent are these aftermaths of Colles' fractures that Bacarn and Kurtzke[1] in a study of 2,000 cases found that "the average (mean) percentage loss of function (disability in all patients with Colles' fractures) was 24 per cent loss of the hand and this increased with the age of the patient and was correlated with the residual deformity." The average duration of treatment was four months, and 96.6 per cent of the patients had physical therapy (usually three times a week); it was the authors' opinion that the physical therapy did not play any appreciable role in altering the final loss of function.

This being true, it behooves us to consider this lesion more seriously. It is agreed that in expert hands the impaction can be broken up by manipulation and a satisfactory reduction can be obtained by mechanical traction and moulding of the fragments.

The difficulty is to maintain the reduction until union is firm. In many cases immobilization in a splint or snug plaster cast with the wrist in pronation, ulnar deviation, and slight flexion is effective. In others which are less stable, increase in the flexion (Cotton-Loder position) may maintain reduction, but this position tends to promote swelling and stiffness in the hand and should not be maintained for more than twelve days. If swelling persists in the hand, an effort must be made to relieve this, even at the risk of losing position of the fragments.

Undoubtedly, in some instances the deformity is never reduced and in others a satisfactory reduction is obtained, but is lost during the application of the splint or cast. In some instances displacement occurs in the splint or cast. Consequently, in severe Colles' fractures it is desirable to obtain roentgenograms immediately after the immobilization and again seven to ten days later, or after the swelling has subsided.

If the position is not satisfactory, a second attempt at reduction should be made, and the surgeon is justified in considering some form of skeletal fixation in order to maintain reduction in the cast. This may be done by transfixing wires or pins through the ulna and metacarpals which are incorporated in the cast, by a medullary pin or nail which is introduced through the radial styloid, or by DePalma's method of a threaded wire which transfixes the ulna and penetrates the major radial fragment to reach the region of the styloid.

In severe lesions such skeletal fixation may be used at the time of the primary reduction, but should not be used by the uninitiated as it is not without danger.

—*J. Albert Key*

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

THE EFFECT OF INCREASED ATMOSPHERIC PRESSURES AND THE INHALATION OF 95 PER CENT OXYGEN AND HELIUM-OXYGEN MIXTURES ON THE VIABILITY OF THE BOWEL WALL AND THE ABSORPTION OF GAS IN CLOSED-LOOP OBSTRUCTIONS*

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INTRODUCTION

WANGENSTEEN[62] in 1931 reported three cases of mechanical small bowel obstruction treated successfully by continuous nasal catheter suction siphonage. Thus began the modern era in the treatment of intestinal obstruction. For the first time, mortality statistics which had been discouragingly high began to decline. Wangensteen and Paine[65] in 1933 reported a mortality of 15.6 per cent in a series of thirty-two patients. Mortality rates in series reported prior to this were commonly in the order of 30 to 60 per cent.[13, 42, 51, 55] McKittrick and Sarris[49] in 1940 were able to report a significant drop in the mortality rate for intestinal obstruction at the Massachusetts General Hospital for the first time in forty years.

This development of continuous suction siphonage for decompression in bowel obstruction was the logical synthesis and practical application of the research of many previous investigators.

The role of swallowed air in bowel obstruction is discussed later. Concomitant with this development, investigators were extending their knowledge as to the toxic factors in obstruction. In 1912 Hartwell and Hoguet[28] clearly demonstrated the lifesaving effect of saline solution given subcutaneously in dogs with high intestinal obstruction, and thirteen years later, in 1925, Gamble and Ross[22] were able to show that death in animals following pyloric obstruction was due simply to fluid and electrolyte loss by severe and continuous vomiting. This, however, does not explain death in low obstructions where the fluid and electrolyte loss is not as great. About 1928 a series of experiments were begun which ultimately showed this "toxic factor" in low obstructions to be explained on the basis of the "mechanical factors" in obstruction; that is,

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increased intraenteric pressures resulting in loss of intestinal viability, increased permeability of the bowel wall resulting in peritoneal contamination, and strangulation of the bowel resulting in blood loss into the strangulated loop and subsequent shock.[63]

Since the advent of continuous suction siphonage, the single most important advance in the treatment of intestinal obstruction has been the development of the long intestinal tube for decompression by Miller and Abbott[43] in 1934, along with its subsequent improved modifications by recent workers.[10, 53, 67]

These developments in the treatment of bowel obstruction, coupled with improved surgical technique, earlier operations, improved x-ray diagnosis, increased knowledge of fluid balance, and the use of antibiotics and whole blood transfusions, bring the treatment of intestinal obstruction up to date. However, since it has been estimated recently[64] that the over-all mortality from intestinal obstruction still runs from 20 to 25 per cent except in clinics in which special interest is manifested, where it may be as low as 10 per cent, further study and improvement are still indicated.

It is the purpose of the present study to investigate methods for increasing gas absorption from the bowel lumen while at the same time retaining the viability and contractility of the wall, either as definitive therapy or as an aid to the passage of a long intestinal tube down the bowel. It is proposed to reevaluate the work of previous investigators[19] on the use of oxygen in high concentrations to hasten the diffusion of trapped gas from the obstructed bowel, as well as to evaluate the use of helium-oxygen mixtures and conditions of increased atmospheric pressures for this same purpose. In the course of the experiments, certain theoretical questions will have to be considered.

Will the use of increased atmospheric pressures increase the rate of diffusion of gas from the obstructed bowel?

From the standpoint of incidence of oxygen intoxication, will the use of high concentrations of oxygen be practical under conditions of increased atmospheric pressure?

Will helium-oxygen mixtures be an effective substitute for oxygen, if intoxication from this latter gas is a factor, in accelerating the absorption of gas from obstructed loops; and, if not, what combination of inhaled gases will be effective?

Finally, what will be the effect of increased atmospheric pressures per se on the maintenance of the viability and contractility of the obstructed bowel wall?

REVIEW OF THE LITERATURE

The Composition of Intestinal Gas.—The gases found in the gut are nitrogen, oxygen, carbon dioxide, methane, hydrogen, hydrogen sulfide, and ammonia. Many workers in this field have analyzed gas from various levels of the intestine with varying results. Hibbard[29] gave the average composition of gases occurring in experimental obstructions of the small bowel as follows:

Nitrogen	70.0 per cent
Carbon dioxide	6.0- 9.0 per cent
Oxygen	10.0-12.0 per cent
Hydrogen	1.0- 3.0 per cent
Methane	0.0- 1 per cent in one case; present in large bowel obstructions, however
Hydrogen sulfide	1.0-10.0 per cent
Volatile basic group	0.5- 5.0 per cent; this group consists of ammonia and the primary and tertiary amines

Pogrund and Steggerda[46] obtained the following analysis on gases from the rectum after a state of equilibrium was attained.

Nitrogen	80.0 per cent
Oxygen	3.0 per cent
Carbon dioxide	7.5 per cent
Residual	9.5 per cent

The Source of Intestinal Gas.—It is generally accepted that intestinal gases arise from swallowed air, from bacterial and chemical processes within the gastrointestinal tract, and by diffusion from the blood stream. It is difficult to assess how much of the accumulated intestinal gas arises from each of these sources. Hibbard and Wangensteen[30] estimated that 68 per cent of the gas is from swallowed air, and 32 per cent arises within the body. Of this last amount, 70 per cent is from diffusion from the blood, and 30 per cent arises within the bowel.

Magendie[41] first described air swallowing in 1813, and in 1860 Planer[45] established large amounts of nitrogen in the upper gastrointestinal tract, suggesting they were due to swallowed air. Although Hoppe-Seyler[31] and others[17, 36, 49] attributed the origin of the stomach gases to fermentation by bacterial and chemical processes, by 1930 it was firmly established by other investigators[2, 32, 68, 69] that the gaseous accumulations in the upper digestive tract have swallowed atmospheric air as their basis. McIver, Benedict, and Cline[39] related the gaseous distention in bowel obstruction in cats to the passage of swallowed air down the intestines, and prevented this distention by ligation of the pylorus. In addition, they were able to prevent postoperative distention in patients by aspirating the stomach twice a day by means of a gastric tube. It has also been adequately shown that gas does not accumulate in experimental closed-loop obstructions from which the swallowed air factor is eliminated. Wangensteen and Rea[66] prevented distention above simple ileal obstructions by dividing the cervical esophagus and turning in the lower portion to prevent the swallowing of air.

The gases generated within the gastrointestinal tract arise from the following sources:

The interaction of gastrointestinal juices.
The enzymatic breakdown of foods.
The bacterial fermentation and putrefaction of foods.

Kantor and Marks[33] stated that a large amount of gas forms in the upper gastrointestinal tract by the interaction of acid gastric juice with the carbonate in the bile and pancreatic juice. V. Bunge[60] estimated this at 6 L. per day in the form of carbon dioxide. The experiments of Hibbard[29] suggest, on the other hand, that the pancreatic and biliary secretions have little to do with the type or quantity of gas formed. There probably is little gas formed by bacterial fermentation and putrefaction in the upper gastrointestinal tract under normal conditions simply because, as has been pointed out by previous investigators,[12, 57] very few bacteria exist in this region. On the other hand, large amounts of carbon dioxide are generated from the bacterial fermentation of starches and sugars in the terminal ileum. Further carbon dioxide is produced in the colon by the breakdown of cellulose. Also produced in the colon are methane and hydrogen. Schwartz[50] showed that 100 Gm. of cellulose decomposed at 38° C. generated 19.5 L. of carbon dioxide, 7.5 L. of methane, and 4.0 L. of hydrogen. Hydrogen sulfide and ammonia are produced in much smaller amounts, along with traces of indole and skatole from the bacterial putrefaction of protein primarily in the colon.

Intestinal flatulence can be influenced markedly by the type of food ingested and also by pathologic conditions existing in the gut. I collected gas in a Rutzen-type ileostomy bag from terminal ileostomies and colostomies, and was able to vary the total volume of gas collected in a twenty-four-hour period, as well as the percentage composition, by variations in the diet. Methane was never collected in significant amounts from ileostomies, thereby placing its production in the colon.

Early investigators[3, 24] believed that gases were actively secreted from the intestinal mucous membrane the same as the mucous secretion itself. However, Haggard and Henderson[27] in 1919 and subsequent investigators[7, 8, 52] demonstrated the diffusion of gases across tissue membranes by injecting gas mixtures into the peritoneal cavity or a specific tissue, and noting that the tension of the carbon dioxide and oxygen in the mixtures soon reached an equilibrium with the tension of these same gases in the blood. By applying this method to the study of bowel gases, Ylppo[69] and others[15, 16] were subsequently able to establish firmly the important role of the diffusion of gases into and out of the bowel in the final composition of intestinal gas. The only gases that can diffuse into the intestine from the blood are nitrogen, oxygen, and carbon dioxide since these are the only gases that are normally present there. The partial pressures of the oxygen and carbon dioxide in the blood are low, however, so that there cannot be much diffusion of these gases into the bowel from the blood. On the other hand, nitrogen exists at a tension of 571.0 mm. Hg, which represents about 80 per cent of the total partial pressure of the blood gases. If any large contribution is to be made to the volume of intestinal gas by diffusion from the blood, it has to come from this source. This takes place slowly because of the slow diffusion rate of nitrogen. McIver and associates[38] injected closed intestinal loops with 20 c.c. of oxygen, and at the end of one hour the gas volume had decreased to 8.5 c.c., 1.8 c.c. of

which was nitrogen which had diffused into the bowel. Since nitrogen already exists at a high partial pressure in the bowel, the only situation in which a significant amount of nitrogen will diffuse into the bowel is that in which the gases being formed in the bowel are formed at a rate faster than they can diffuse from the bowel, keeping the partial pressure of nitrogen low. This situation is more likely to occur with the slowly diffusing gases, methane and hydrogen, and probably does occur for short periods of time.

The Absorption of Intestinal Gases.—Zuntz and Tacke[70] determined from experiments on rabbits that ten to twenty times more intestinal gas is expelled by way of the blood stream and lungs than through the anus. Ylppo,[69] Schoen,[48] and later McIver and associates[38] studied the diffusion rates of gases from the bowel. McIver's results are summarized in Fig. 1. Pogrund and Steggerda[46] obtained comparable diffusion rates for nitrogen, oxygen, and carbon dioxide. They also showed that these gases diffuse from the bowel until an equilibrium is reached with the gases in the blood.

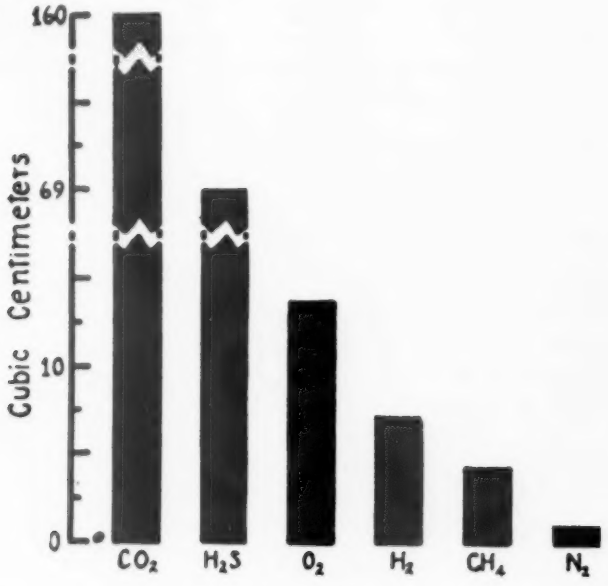


Fig. 1.—Comparative absorption rates of the common intestinal gases from closed-loop obstructions in cats. (From McIver and associates.[38])

The rates of diffusion of the bowel gases from the intestine are determined by purely physical and chemical principles:

The partial pressure gradient of the gases across the intestinal mucous membrane, that is, between the bowel lumen and the blood.

The absorption coefficient of the gases in the blood.

The molecular weight (density) of the gases involved.

The area of surface contact between the gases and the permeable membrane, and also the thickness of the membrane.

The diffusion velocity of any gas is inversely proportional to the square root of its molecular weight, and directly proportional to its absorption coefficient in the medium into which it is diffusing.

Anderson and Ringsted[1] gave the following figures for the absorption coefficients of the common bowel gases in the blood. (Expressed as cubic centimeters of gas in 1 c.c. of blood at 38° C., and 760 mm. of pressure.)

Nitrogen	0.012 c.c.
Hydrogen	0.016 c.c.
Methane	0.022 c.c.
Oxygen	0.022 c.c.
Carbon dioxide	0.50 c.c.
Hydrogen sulfide	1.66 c.c.

The relative diffusion velocities of these same gases into blood, again making nitrogen equal to 1, were given by Anderson and Ringsted as follows:

Nitrogen	1.0
Oxygen	1.8
Methane	2.5
Hydrogen	5.0
Carbon dioxide	35.0
Hydrogen sulfide	130.0

McIver's[38] values for the absorption of gases from a closed loop of cat's intestine are the following:

Nitrogen	1.5 c.c. per hour
Methane	5.0 c.c. per hour
Hydrogen	7.0 c.c. per hour
Oxygen	18.0 c.c. per hour
Hydrogen sulfide	69.0 c.c. per hour
Carbon dioxide	160.0 c.c. per hour

The diffusion of hydrogen, methane, and hydrogen sulfide from the bowel is unopposed by a partial pressure of these gases existing in the blood. The reason hydrogen sulfide diffuses so rapidly from the bowel is its high solubility coefficient in the blood as compared to the other gases.

Nitrogen, oxygen, and carbon dioxide, on the other hand, have to diffuse against the partial pressure of these same gases existing in the blood. Glasser[25] gave the following values for gas tensions in venous blood.

	Partial Pressures (mm. Hg)	*Percentages*
Nitrogen	572.0	82.0
Oxygen	38.0	5.5
Carbon dioxide	42.0	6.0
Water vapor	47.0	6.5
	699.0	100.0

The diffusion of oxygen and carbon dioxide from the bowel is higher than can be explained on purely physical principles because both of these gases are

in physical solution only to a small degree, but exist primarily in chemical combination in the blood. Hence, carbon dioxide diffuses from the bowel faster than hydrogen sulfide, and oxygen faster than either hydrogen or methane, which is the opposite of what is expected from the relative diffusion velocities as given by Anderson and Ringsted.[1]

Nitrogen leaves the bowel slowly, not only because of its low diffusion velocity based on its molecular weight and low absorption coefficient in blood, but also because the blood, tissues, and alveolar air are already saturated with nitrogen, giving a low partial pressure gradient across the intestinal mucous membrane. Once nitrogen enters the bowel, as in swallowed air (partial pressure of nitrogen in atmospheric air is 597.0 mm. Hg), it cannot be reabsorbed in significant amounts under the usual existing conditions.

It was pointed out earlier that intestinal gas consists of 75 to 80 per cent nitrogen. The problem of increasing the absorption of intestinal gases from the lumen of the bowel, therefore, resolves itself into the problem of increasing the diffusion of nitrogen from the bowel. Since neither its coefficient of absorption in the blood nor its molecular weight can be changed to hasten the absorption of nitrogen, the only way this can be accomplished is by increasing the partial pressure gradient of nitrogen across the intestinal mucous membrane through the inhalation of a nonnitrogen-containing gas such as 100 per cent oxygen.

Fine and associates[18-20] investigated this thesis. They found that 16 per cent of the volume of nitrogen injected into the intestine of cats with the pylorus and terminal ileum tied off was absorbed in eighteen hours when cats breathed atmospheric air; whereas, when they breathed 95 per cent oxygen, 61 per cent of the nitrogen was absorbed. They also reported five cases of patients with clinical distention responding well to the inhalation of 95 per cent oxygen in a period of six to twelve hours. The experimental findings were confirmed by Paine,[44] Anderson and Ringsted,[1] and Troell.[58] The latter also applied conditions of increased atmospheric pressure and increased concentrations of carbon dioxide in the inhaled gas mixture to hasten the absorption of nitrogen.

The use of high concentrations of oxygen for prolonged periods of time at normal or increased atmospheric pressures is not without danger, however.

Oxygen Intoxication.—The symptoms of oxygen intoxication brought on by breathing oxygen at high pressures differ from those brought on by breathing oxygen at atmospheric pressure. Paul Bert[6] was the first to study the effects of oxygen at increased atmospheric pressures in experiments utilizing both superoxygenated air and ordinary air at high pressures. His animals died in convulsions, and these convulsive symptoms began to appear at an oxygen tension of 2,280 mm. Hg, corresponding to 100 per cent oxygen at 3 atmospheres pressure or ordinary air at 15 atmospheres pressure.

J. L. Smith,[54] working with mice, described an entirely different aspect of oxygen intoxication. He found that mice exposed to lower ranges of increased oxygen tensions (0.7 to 3 atmospheres) died from pulmonary congestion, edema, and pneumonia.

It is generally considered that a concentration of oxygen in excess of 60 per cent, 0.6 atmosphere, is necessary to produce symptoms. In Smith's experiments, no symptoms developed in a period of eight days with an average oxygen concentration of 41.6 per cent; whereas, with 70 to 80 per cent oxygen, some of the mice died within four days from congestion of the lungs. Comroe and associates[11] found that 35 per cent of the subjects breathing 75 per cent oxygen developed symptoms of oxygen intoxication within twenty-four hours, while none of the subjects breathing 50 per cent oxygen developed symptoms. Paine, Lynn, and Keys,[44] studying the prolonged administration of 95 per cent oxygen to dogs, found a great individual variation in their susceptibility to oxygen intoxication, the dogs dying in periods varying from six to ninety-six hours. Interruption of the administration of the oxygen increased the ability of the dogs to withstand the high concentration. Becker-Freyseng and Clamann[4] subjected themselves to 90 per cent oxygen at atmospheric pressure and found no ill effects in the first twenty-four hours, but soon after this they developed symptoms. Behnke and associates,[5] studying healthy men between the ages of 20 and 40 breathing pure oxygen, gave the following limits of tolerance: four hours at 1 atmosphere, three hours at 2 atmospheres, and two hours at 3 atmospheres pressure. Two subjects breathed 100 per cent oxygen at 4 atmospheres for forty-five minutes. One of them developed a convulsive seizure, and the other, sudden blanching, sweating, and a fall in blood pressure.

Increasing the concentration of carbon dioxide in the inspired gas mixture increased the susceptibility to oxygen intoxication.

The symptoms of oxygen intoxication have been described by various authors[4, 5, 26] as nausea and vomiting, joint pains, increased body temperature, substernal burning, dyspnea, blanching, sweating, increased pulse rate, contraction of visual fields with loss of visual acuity, dizziness, stupefaction, and, finally, convulsive seizures.

Karsner[34] made a thorough study of the pathologic effects of high concentrations of oxygen at atmospheric pressure. He described marked congestion, edema, epithelial degeneration and desquamation, fibrin formation, and fibrinous pneumonitis in animals exposed to high concentrations of oxygen for forty-eight hours or more. Paine[44] described these same changes in the lungs and also dilatation of the stomach, contraction of the spleen, and congestion and hyperemia of the kidneys and liver.

METHODS OF STUDY

For these experiments, a compression chamber was built measuring seven feet in length by three feet in diameter with an internal capacity of approximately forty-five cubic feet (Figs. 2 and 3). Four glass observation ports were constructed into the side of the tank, along with a plastic x-ray port on top of the chamber. Directly opposite the x-ray port there was a mobile cassette container in the grid floor of the tank so that x-ray films could be taken while the chamber was pressurized.

The compressed air was supplied by a 1½ horsepower compressor, the oxygen and helium-oxygen mixtures being obtained in the required percentages

from cylinders. A bleed-off valve and a gauge measuring the pressures within the tank were mounted on top of the compression chamber.

The gas flow through the tank was easily controlled by adjusting the bleed-off valve on the tank against the flow control valve on the intake line

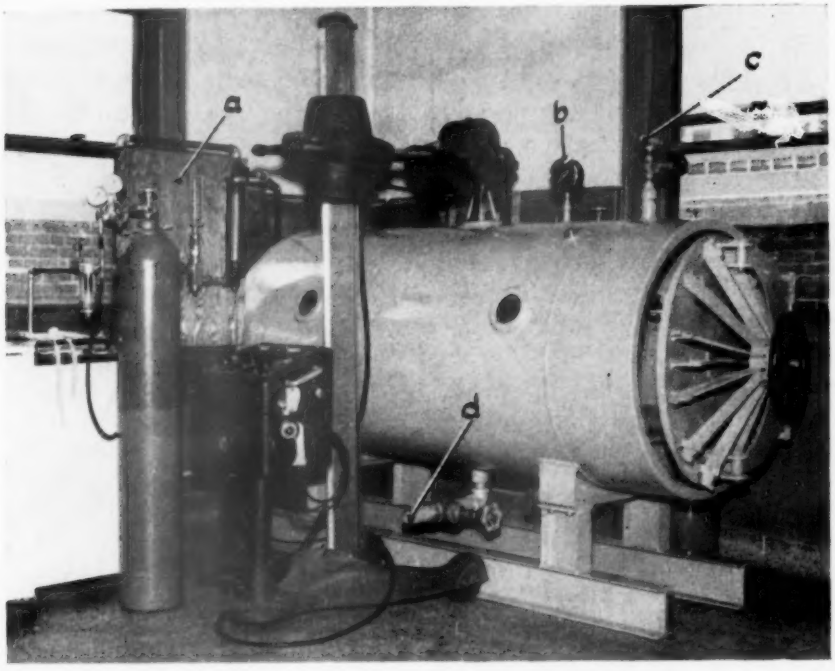


Fig. 2.—External view of compression chamber showing the portable x-ray unit in place. *a*, Control panel; *b*, pressure gauge; *c*, bleed-off valve; *d*, drain.

Fig. 3.—Internal view of compression chamber. The large cooling coils are seen along both sides of the chamber. (From Cross, F. S.: Proc. Surg. Forum, Clin. Congress Am. Coll. Surgeons, 1952, Philadelphia, 1953, W. B. Saunders Company.)

until the desired rate of flow was attained as measured on the flowmeter on the intake line at the pressure desired, as measured on the chamber pressure gauge. Uniform pressures and rates of gas exchange within the chamber could be maintained for many hours in this manner whether compressed air or cylinder gas was used in the experiment.

All experiments except those conducted in air at a pressure of 1 atmosphere were carried out in the compression chamber. Two closed small bowel loops 75 cm. long were made in healthy mongrel dogs under Nembutal anesthesia, weighing 8 to 11 kilograms, by ligating the bowel in continuity with a double strand of 000 silk after stripping the bowel clean of its contents. One hundred fifty cubic centimeters of room air was injected into each loop using an oiled 50 c.c. syringe connected to a three-way stopcock and a No. 18 gauge needle.

The distention of the loops after the injection of the gas ranged from moderate to a severe degree with blanching of the gut wall. Intraenteric pressures were taken in thirty-five instances and found to range from 8 to 98 cm. of water, all but five of the pressures being in the range of 10 to 30 cm. of water.

Four dogs were run at a time, and all dogs were in the tank and pressurized within one and one-half hours after the injection of the loops in the first dog. During this interval there was no appreciable loss of gas from the loops. When oxygen and helium-oxygen mixtures were used, the chamber was flushed out with the gas mixture until the proper percentage in the tank was reached, and the tank was then pressurized to the desired working pressure. During the experiments, the chamber was continuously flushed with the experimental gas mixture. Oxygen and carbon dioxide percentages within the chamber were checked every one-half to one hour with a Scholander gas analyzer. In many instances, soda lime was used in the chamber to help keep the carbon dioxide at 0 per cent. Oxygen within the chamber averaged very close to 95 plus or minus 2 per cent in the total course of the experiments in which this gas was utilized. Helium percentages in the chamber ran within a range of 5 per cent less than the desired 60 or 80 per cent.

At the end of each experiment the dogs were reanesthetized, the residual gas in the bowel was aspirated, and the per cent of absorption from each loop was calculated. The bowel was also observed for any loss of viability, and the amount of fluid which had collected in each loop was measured. All dogs were observed for signs of oxygen intoxication when this gas was inhaled. Samples of the residual gas in the loops were collected in many instances and analyzed by means of the mass spectrometer.

The following experiments were set up:

Gas Absorption Studies:

Group 1. Dogs with closed-loop obstructions breathing air at pressures of 1 to 4 atmospheres for periods of six to twenty-four hours.

Group 2. Dogs with closed-loop obstructions breathing 95 per cent oxygen* at pressures of 1 to 2.5 atmospheres for periods of six to twelve hours.

Group 3. Dogs with closed-loop obstructions breathing helium-oxygen mixtures at pressures of 1 to 2 atmospheres for periods of six to twenty-four hours.

Group 4. Dogs with closed-loop obstructions breathing 95 per cent oxygen, air, and helium-oxygen mixtures in various combinations at a pressure of 2 atmospheres for periods of twelve to twenty-four hours.

The Effect of Increased Atmospheric Pressures on the Viability of the Bowel in Closed-loop Obstructions:

(a) The effect of increased pressures on the maintenance of viability of the bowel.

(b) The effect of increased pressures on the contractility of the obstructed bowel.

RESULTS

Preliminary work with the compression chamber emphasized especially technical details concerned with the use of the tank and some of the physical problems connected with experiments in compressed air. Without discussing the matter in any great detail, suffice it to say that as long as such factors as temperature, humidity, and carbon dioxide accumulation within the tank were well controlled, the dogs tolerated the pressures used (1 to 4 atmospheres) very well. Dogs were subjected to continuous pressures of 4 atmospheres (forty-five pounds per square inch) for twenty-four hours, and intermittent pressures of 3 to 4 atmospheres (about one and one-half hours at normal pressure out of each twenty-four-hour period) for ninety-two hours without difficulty.

Gas Absorption Studies in Closed-loop Obstructions.—

Group 1: This group of experiments was designed primarily to determine the effect of pressure per se on the absorption of injected air from closed-loop obstructions using dogs breathing air at pressures of 1 to 4 atmospheres for periods of six to twenty-four hours. These results are summarized in Table I.

TABLE I. PERCENTAGE OF GASEOUS DIFFUSION FROM CLOSED-LOOP OBSTRUCTIONS IN DOGS BREATHING AIR

PRESSURE (ATMOS.)	TIME (HR.)	NO. OF LOOPS	MEAN PER CENT OF ABSORPTION	DIFFERENCE BETWEEN MEANS	P
1	6	10	10.8		
				0.4	
1	24	22	10.4		
				16.6	< 0.0001
2	24	22	27.0		
				6.8	< 0.01
3	24	20	33.8		
				7.0	< 0.01
4	24	20	40.8		

It is interesting to note that after six hours at 1 atmosphere pressure, an average of 10.8 per cent of the injected air had diffused from the loops, and that no further increase in the absorption occurred in the twenty-four hours.

*Ninety-five per cent oxygen refers to 95 per cent oxygen and 5 per cent nitrogen.

At 2 atmospheres pressure, 27.0 per cent of the injected gas was absorbed, an increase of 16.6 per cent. At pressures of 3 to 4 atmospheres, 33.8 per cent and 40.8 per cent, respectively, of the injected gas was absorbed, an average increase of about 7.0 per cent for each increase of 1 atmosphere above 2 atmospheres pressure. This increase in absorption with increasing pressures represents a statistically significant difference.

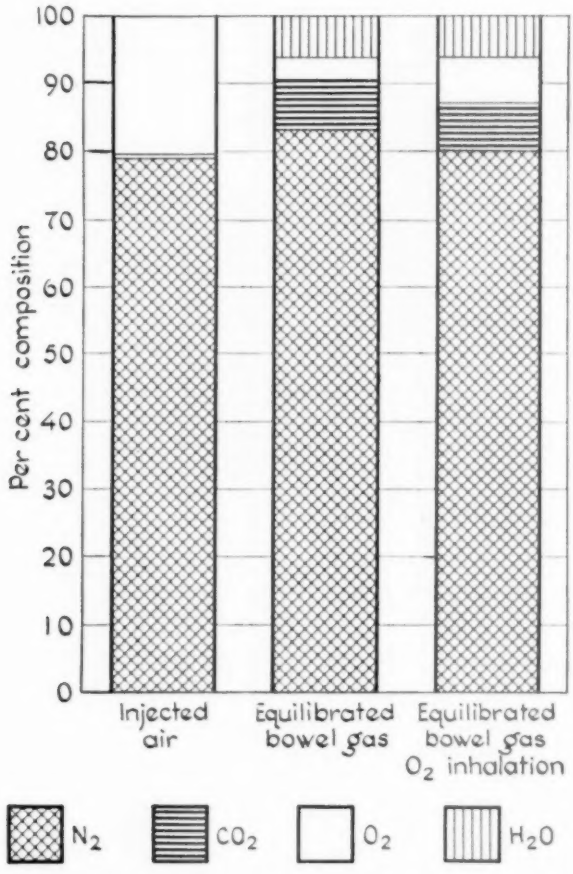


Fig. 4.—Comparison of the percentage composition of initially injected air with equilibrated bowel gas aspirated from closed-loop obstructions in dogs breathing air and 95 per cent oxygen.

No matter what gas is injected into the closed loops, nitrogen, hydrogen, or air, certain initial changes in volume take place because of the equilibration between the partial pressures of the gases in the bowel and those in the tissues and blood stream. With nitrogen and hydrogen, the initial volume in the closed loops will be increased because of the diffusion of carbon dioxide and oxygen in the bowel. When dry gases are injected, there is also an increase in the water vapor to a partial pressure of 47 mm., which is a constant value. When air is injected into the closed loops, carbon dioxide diffuses into the bowel, but oxygen diffuses out of the bowel in a greater amount than the carbon dioxide entering it. Again the partial pressure of the water vapor increases. The over-all effect is a slight decrease in volume, which in this

study has been calculated to be 5.0 c.c. This 5.0 c.c. constitutes 3.4 per cent of the originally injected gas volume. If the rate of diffusion of nitrogen is calculated as cubic centimeters per hour for the six-hour period of diffusion, it is found that the nitrogen diffused from the bowel at a rate of 1.5 c.c. per hour, which is similar to the rate obtained by McIver and associates.[38] Fig. 4 compares the percentage composition of the injected air with the composition of the residual gas in the obstructed bowel after coming into equilibrium with the blood gases. The partial pressures of the nitrogen, carbon dioxide, and water vapor increase, while the partial pressure of the oxygen decreases. After these initial adjustments are made, the rate of absorption of the gas from the closed-loop obstructions is controlled by the slowly diffusing nitrogen, and the subsequent loss in volume consists largely of nitrogen, since this gas constitutes about 80 per cent of the gas in the loops.

Group 2: The inhalation of 95 per cent oxygen increased the diffusion rate of the injected air from the closed-loop obstructions markedly when compared to the inhalation of air, and again the beneficial effect of increased pressures on absorption rates was well demonstrated (Table II).

TABLE II. PERCENTAGE OF GASEOUS DIFFUSION FROM CLOSED-LOOP OBSTRUCTIONS IN DOGS BREATHING 95 PER CENT OXYGEN

PRESSURE (ATMOS.)	TIME (HR.)	NO. OF LOOPS	MEAN PER CENT OF ABSORPTION	DIFFERENCE BETWEEN MEANS	P
1	6	23	37.5	7.3	< 0.0001
2	6	30	44.8		
2.5	6	30	44.3		
1	12	19	46.9	16.4	< 0.0001
2	12	17	63.3		

In a six-hour period at 2 atmospheres pressure, 44.8 per cent of the gas was absorbed, compared to 37.5 per cent at 1 atmosphere pressure, an increase of 7.3 per cent. At 2.5 atmospheres, no further increase in absorption took place in the six-hour period. With the inhalation of 95 per cent oxygen at 1 atmosphere for twelve hours, 46.9 per cent of the bowel gas was absorbed; whereas, at 2 atmospheres for the same length of time, 63.3 per cent of the injected gas was absorbed, an increase of 16.4 per cent. This is approximately twice the increase as for the six-hour period at similar pressures, which is what might be expected.

Essentially the same amount of gas was absorbed when oxygen was inhaled at 1 atmosphere for twelve hours (46.9 per cent) as at 2 atmospheres for six hours (45.8 per cent). As the end results are approximately the same, the latter schedule is not only six hours shorter but also has the advantage gained from the beneficial effects of pressure per se on the bowel. There were large amounts of fluid (150 to 300 c.c.) added to four of the loops at a pressure of 1 atmosphere in the twelve-hour period; whereas, none of the loops contained fluid at 2 atmospheres pressure in the six-hour period.

Diffusion of gas from closed-loop obstructions was best in those dogs breathing 95 per cent oxygen for twelve hours at 2 atmospheres pressure, but this schedule proved to be impractical because of the high incidence of oxygen intoxication (100 per cent).

The general problem of oxygen intoxication formed a very interesting side light in these gas absorption experiments because it constituted a complication which compromised the very gas-pressure-time combinations that gave the best results. The symptoms observed in the dogs studied in this part of the experiment can be divided into the following categories:

Mild —Early symptoms consisting of restlessness and slight dyspnea.

Moderate—More severe dyspnea, grunting respirations, frothing at the mouth, wretching, and lethargy.

Severe —Severe dyspnea with grunting respirations, semiconsciousness to complete unconsciousness, eyes glassy and fixed, stiffness and rigidity of the limbs, inability to walk, and, at times, convulsions.

From studying Table III, it can be seen that the dogs tolerated 95 per cent oxygen for six hours at 2 atmospheres pressure and for twelve hours at 1 atmosphere very well. When the pressure was increased above 2 atmospheres, or when the time of exposure at 2 atmospheres extended beyond six hours, the incidence of oxygen intoxication rose significantly. Of twelve dogs exposed from nine to twelve hours at 2 atmospheres pressure, 100 per cent developed symptoms of oxygen intoxication, and 90 per cent of twenty dogs exposed for six hours at 2.5 atmospheres developed symptoms. None of the dogs exposed to 2 atmospheres of oxygen for six hours, or to 1 atmosphere of oxygen for twelve hours, developed symptoms.

TABLE III. INCIDENCE OF OXYGEN INTOXICATION IN DOGS BREATHING 95 PER CENT OXYGEN ALONE OR IN COMBINATION WITH AIR AND HELIUM-OXYGEN MIXTURES

GAS MIXTURE (%)	DURATION (HR.)	PRESSURE (ATMOS.)	NO. OF DOGS	NO. WITH SYMPTOMS	SEVERITY OF SYMPTOMS
O_2 95	6	1	12	0	
O_2 95	6	2	20	0	
O_2 95	6	2½	20	18	Moderate to very severe
O_2 95	9	2	4	4	Severe
O_2 95	12	1	8	0	
O_2 95	12	2	8	8	Very severe
He-O_2 (80-20)	6	2	8	0	
He-O_2 (60-40)	6	2	12	0	
He-O_2 (80-20) (60-40)	18 to 24	2.5	16	0	
He-O_2* (60-40)	6	2	15	6	Four dogs with mild and two with moderate symptoms
O_2 95	6				
O_2 95*	6	2	4	2	Both dogs had mild symptoms
He-O_2 (80-20)	6				
O_2 95	6				
O_2 95*	6	2	6	2	Both dogs had mild symptoms
Air	6				
O_2 95	6				
O_2 95*	6	2	9	9	Seven dogs with severe and two with mild symptoms
He-O_2 (60-40)	6				
O_2	6				

*These gas mixtures inhaled in succession for six-hour periods.

All the dogs in the oxygen inhalation experiments were sacrificed at the end of each experiment, and the lungs were examined grossly, and microscopically if gross changes were present, or if the dog had clinical symptoms of oxygen intoxication. On gross examination, the involved lungs were edematous and showed varying degrees of consolidation. This consolidation was spotty in its distribution and was characteristically most marked at the periphery of the lobes, varying from dark red to almost black in appearance.

Microscopically the changes ranged from slight edema and congestion of the alveolar walls, to the marked edema and infiltration of the alveoli themselves, going on to the extreme consolidation shown in Fig. 5. Most of the cellular infiltration consisted of red blood cells. There was no consistent correlation found between the degree of pulmonary changes at autopsy and the severity of the symptoms observed before death.

Fig. 5.—Severe changes in lung of Dog 1646 from breathing 95 per cent oxygen for six hours at 2.5 atmospheres pressure.

Group 3: In an attempt to overcome the problem of oxygen intoxication with prolonged exposures to 95 per cent oxygen at increased atmospheric pressures, and to help obviate any difficulty over problems of decompression, helium-oxygen mixtures were used as the gas inhaled. Two such mixtures were tested, employing helium and oxygen in the ratio of 80 per cent-20 per cent, and 60 per cent-40 per cent.

Although oxygen intoxication was not a factor in the dogs breathing these helium-oxygen mixtures, the absorption rates of the gas from the obstructed loops were disappointingly low (Table IV). In a six-hour period, at either 1 or 2 atmospheres, the absorption rates were essentially the same for the 80 per cent-20 per cent mixture as for the 60 per cent-40 per cent mixture,

being approximately 20 per cent in six hours at 1 atmosphere pressure, and 28 per cent in six hours at 2 atmospheres pressure. This represents an increase of 8.0 per cent for the 1 atmosphere increase in pressure.

TABLE IV. PERCENTAGE OF GASEOUS DIFFUSION FROM CLOSED-LOOP OBSTRUCTIONS IN DOGS BREATHING HELIUM-OXYGEN MIXTURES

GAS MIXTURE (%)	PRESSURE (ATMOS.)	TIME (HR.)	NO. OF LOOPS	MEAN PER CENT OF ABSORPTION	DIFFERENCE BETWEEN MEANS	P
$He-O_2$ (80-20)	1	6	10	19.9	8.4	<0.01
	2	6	17	28.3		
$He-O_2$ (60-40)	1	6	10	21.1	6.5	<0.001
	2	6	22	27.7		
$He-O_2$ (80-20)	2.5	18	8	31.0		
$He-O_2$ (80-20)	2.5	24	8	39.4	5.0	>0.05
$He-O_2$ (60-40)	2.5	24	7	46.4		

The explanation for these poor absorption rates with the helium-oxygen mixtures lies in the fact that when the residual gas in the closed-loop obstructions was analyzed, significant amounts of helium were found. In other words, as the nitrogen diffused out of the bowel, the helium diffused in. The amount of helium in the residual gas was directly proportional to the length of exposure. After a six-hour period, no matter which concentration of helium was inhaled, the residual gas in the closed loop contained about 15 per cent helium. This increased to as much as 39.8 per cent in a twenty-four-hour period when the 60 per cent-40 per cent mixture was inhaled. Furthermore, the helium, once in the bowel, was slow to diffuse out again when a nonhelium-containing gas was again inhaled. From Table V, it can be seen that when a 60 per cent-40 per cent oxygen mixture was inhaled for six hours, followed by the inhalation of 95 per cent oxygen for six hours, there was still 16 per cent helium in the bowel after the six-hour period of oxygen inhalation.

Although helium is a gas of low molecular weight which favors rapid diffusion, its rate of diffusion from the bowel is slow because of its low solubility coefficient in the blood (0.0087), as compared to nitrogen (0.0127).

Group 4: In this group of experiments, air and helium-oxygen mixtures were used in sequence with oxygen in order to extend the usefulness of any one of the gases. The percentage of gas absorbed from the closed loops when 60 per cent helium–40 per cent oxygen was inhaled for six hours at 2 atmospheres pressure, followed by 95 per cent oxygen under the same conditions, was 48.5 per cent (Table VI). Again this is not much better than the absorption with 95 per cent oxygen at 2 atmospheres for only six hours (44.8 per cent).

When oxygen and helium-oxygen mixtures were alternated at six-hour intervals for a total of eighteen hours at 2 atmospheres pressure, 60.3 per cent to 63.9 per cent of the gas in the obstructed loops was absorbed. When air was substituted for the helium-oxygen mixture in the middle six-hour period, 63.2

per cent of the gas diffused from the obstructed bowel. Since the rate of absorption is approximately the same, the latter combination is much more satisfactory because air is infinitely cheaper than the helium-oxygen mixture.

TABLE V. PERCENTAGE OF HELIUM DIFFUSING INTO CLOSED-LOOP OBSTRUCTIONS IN DOGS BREATHING HELIUM-OXYGEN MIXTURES

GAS MIXTURE (%)	PRESSURE (ATMOS.)	TIME (HR.)	PER CENT OF HELIUM IN LOOPS
$He-O_2$ (80-20)	1	6	14.8
$He-O_2$ (80-20)	2	6	15.5
$He-O_2$ (60-40)	2	6	14.5
$He-O_2$* (60-40) O_2 95	2	6	16.0
$He-O_2$ (80-20)	1	10	17.6
$He-O_2$ (80-20)	2.5	18	33.8
$He-O_2$ (80-20)	2.5	24	37.2
$He-O_2$ (60-40)	2.5	24	39.8

*Gas sample taken after 95% oxygen had been inhaled for 6 hours.

TABLE VI. PERCENTAGE OF GASEOUS DIFFUSION FROM CLOSED-LOOP OBSTRUCTION IN DOGS BREATHING VARIOUS GAS MIXTURES IN SEQUENCE

GAS MIXTURE*	PRESSURE (ATMOS.)	TIME (HR.)	NO. OF LOOPS	MEAN PER CENT OF ABSORPTION	DIFFERENCE BETWEEN MEANS	P
Series I	2	12	30	48.5		
					11.8	<0.001
Series II	2	18	10	60.3		
					3.6	>0.05
Series III	2	18	19	63.9		
Series IV	2	18	12	63.2		

*Series I $He-O_2$ (60–40) for 6 hr.
O_2 (95) for 6 hr.

Series II O_2 (95) for 6 hr.
$He-O_2$ (80–20) for 6 hr.
O_2 (95) for 6 hr.

Series III O_2 (95) for 6 hr.
$He-O_2$ (60–40) for 6 hr.
O_2 (95) for 6 hr.

Series IV O_2 (95) for 6 hr.
Air for 6 hr.
O_2 (95) for 6 hr.

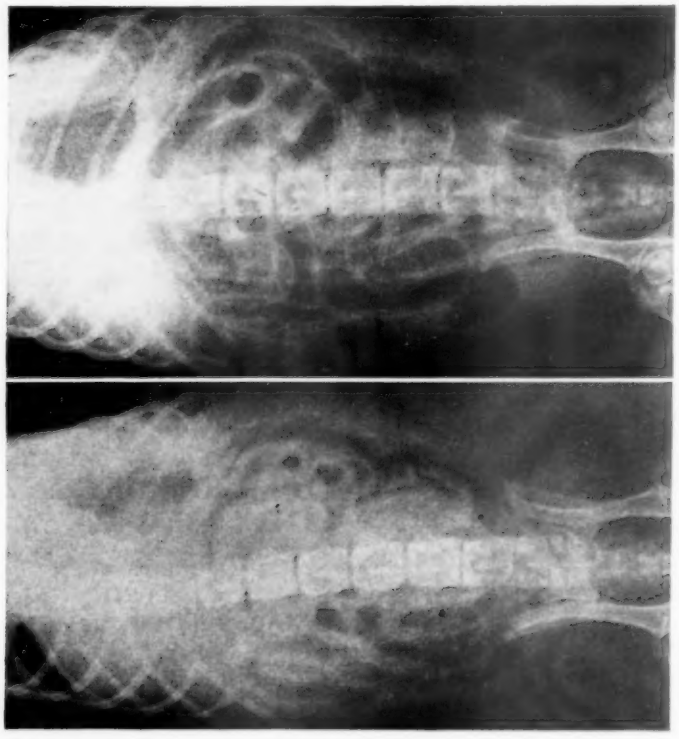
Oxygen intoxication was no significant problem in those experiments using air or 80 per cent helium-20 per cent oxygen intermittently with oxygen at 2 atmospheres; whereas, it was a definite problem when 60 per cent helium–40 per cent oxygen mixtures were used (Table III). All the dogs in the latter group had symptoms ranging from mild to severe (Table III). This can be explained by the fact that even in the interval in which 60 per cent helium–40 per cent oxygen was inhaled, the partial pressure of oxygen was 0.8 atmosphere, which exceeds the accepted safe upper limit of 0.6 atmosphere.

Effect of Increased Pressures on the Maintenance of Viability of the Bowel.—The observations in this group of experiments were made on closed-

loop obstructions similar to those used in the absorption experiments. They were also distended with 150 c.c. of air.

The effect of increased atmospheric pressures per se on the condition of the bowel in such closed-loop obstructions is one of the most interesting aspects of this study. According to Boyle's law, the volume of gas is inversely proportional to the pressure. If the pressure is doubled, the volume of the gas is reduced to one-half. Fig. 6 illustrates this effect on the gas volume in the obstructed bowel of a dog at 1 and 3 atmospheres pressures, respectively. The decreased distention of the bowel at 3 atmospheres compared to 1 atmosphere pressure is apparent, and the benefits of this decreased distention are clear cut.

A.



B.

Fig. 6.—Degree of distention of a closed-loop obstruction in a dog at 1 atmosphere pressure (*A*) compared to the same dog at 3 atmospheres pressure (*B*). Since the degree of distention is inversely proportional to the atmospheric pressure, the bowel is about one-third as distended at 3 atmospheres as at 1 atmosphere. (From Cross, F. S.: Proc. Surg. Forum, Clin. Congress Am. Coll. Surgeons, 1952, Philadelphia, 1953, W. B. Saunders Company.)

In dogs with closed-loop obstructions containing 150 c.c. of injected air and maintained for twenty-four hours in air under 2 to 4 atmospheres pressure, the general tone and viability of the bowel were well preserved (Table VII). In only six of a total of sixty, or 10 per cent, of these obstructed loops, were there any signs of impairment of viability or normal function as evidenced by the following criteria:

Edema of the bowel wall and fluid collection in the lumen.

Flabby distention due to loss of tone.

Areas of impending or frank gangrene, with or without perforation.

TABLE VII. EFFECT OF INCREASED PRESSURE ON VIABILITY OF CLOSED INTESTINAL LOOPS

PRESSURE (ATMOS.)	TIME (HR.)	TOTAL OBSTRUCTED LOOPS	IMPAIRED VIABILITY	PER CENT
2-4	24	60	6	10
1	24	27	19	70

Furthermore, the changes in the bowel of these six pressurized dogs were of a minimal nature.

One of the dogs had ecchymotic areas present, while the other five dogs had merely fluid collection in the bowel lumen.

TABLE VIII. SUMMARY IN LONG-TERM SURVIVAL EXPERIMENTS IN DOGS WITH CLOSED-LOOP OBSTRUCTIONS AT ATMOSPHERIC PRESSURE

DOG	PRESSURE (ATMOS.)	DURATION (HR.)	IMPAIRED VIABILITY IN LOOPS*	FLUID IN LOOPS (C.C.)	PER CENT OF GAS ABSORBED	COMMENT
1336	1	24	One loop perforated, other with marked changes	? 50	 33	Dog dead of peritonitis
128	1	12	Moderate loss in both loops	350 15		Spontaneous death of unknown cause; no perforations; edema, loss of tone, and dark areas in bowel
118	1	66	Marked changes in both loops	25 400	13.3 33.3	Dog sacrificed; free fluid in peritoneal cavity; gangrenous areas in bowel
132	1	66	Minimal Minimal	50 400	33.3 40.0	Dog sacrified at 66 hr.
158	1	66	Marked changes in both loops	280 300	30.0 36.6	Dog sacrificed because near death; free fluid in peritoneal cavity; gangrene of bowel wall
145	1	42	Marked changes in both loops	310 30		Dog died; free fluid in peritoneal cavity
1386	1	43	One loop perforated, other with marked changes	? 250		Dog dead of peritonitis
1398	1	43	Severe changes in both loops	400 120	30.6 36.6	Sacrificed because near death; edema, loss of tone, and gangrene of both loops
Average fluid accumulation in nonperforated loops				213 c.c.		
Average gas absorption					31.8%	

*Two closed loops 75 cm. in length in each dog.

In dogs maintained for twenty-four hours under only 1 atmosphere pressure, the results were quite different. Nineteen of twenty-seven obstructed loops in these dogs showed a loss of viability or normal function by the same criteria.

In addition, these changes were of a more severe nature than those found in the dogs maintained under increased pressure, being characterized by marked loss of tone and areas of frank gangrene.

In long-term experiments the contrast was equally marked. Only one of eight dogs with similar obstructions survived for sixty-six hours without severe changes in the bowel wall (Table VIII). The other seven dogs had impending or frank gangrene of the bowel wall, and in six of these dogs there was free fluid in the peritoneal cavity.

Under 3 to 4 atmospheres pressure, however, six of eight dogs survived over sixty-six hours without gangrene of the obstructed loops. One of the surviving dogs was sacrificed after ninety-two hours, at which time the bowel was in perfect condition, and 92 per cent of the injected gas was absorbed (Table IX). Of the two dogs that died, one died at thirty-six hours with the obstructed bowel entirely normal, and the other died at seventy-two hours with edema, loss of tone, and ecchymotic areas in the bowel, but no frank gangrene or perforation.

TABLE IX. SUMMARY OF LONG-TERM SURVIVAL EXPERIMENTS IN DOGS WITH CLOSED-LOOP OBSTRUCTIONS AT INCREASED ATMOSPHERIC PRESSURES

DOG	PRESSURE (ATMOS.)	DURATION (HR.)	IMPAIRED VIABILITY IN LOOPS*	FLUID IN LOOPS (C.C.)	PER CENT OF GAS ABSORBED	COMMENT
1321	4	66	No	25	42.0	Dog sacrificed at 66 hr.
				0	63.4	
1305	4	66	No	10	60.0	Dog sacrificed at 66 hr.
				10	87.0	
1365	4	66	No	10	78.6	Dog sacrificed at 66 hr.
				140	93.5	
1378	3	73	No	0	66.6	Dog sacrificed at 66 hr.
				0	86.6	
1377	3	92	No	25	90.0	Dog sacrificed at 66 hr.
				25	93.5	
1374	3	78	Minimal in both loops	190		Spontaneous death of unknown cause; no perforation of either loop; only edema, loss of tone, and dark areas present in bowel
				190		
1376	3	36	No	0		Spontaneous death of unknown cause; bowel entirely normal
				0		
Average fluid accumulation per closed loop				49 c.c.		
Average gas absorption					76.1%	

*Two closed loops 75 cm. in length in each dog.

The Effect of Increased Pressures on the Contractility of the Obstructed Bowel.—In a series of experiments utilizing a standard-sized balloon in a closed-loop obstruction, it was determined that the contractility of the obstructed bowel is enhanced under conditions of increased atmospheric pressures. Fig. 7 illustrates the kymograph tracings obtained by this method. It is seen that the effective contractions of the bowel are diminished when the loop is distended at 1 atmosphere pressure as compared to the contractions in the same loop prior to its distention. However, when the pressure is increased to 2 atmospheres, the distention of the loop is decreased, and the ability of the bowel to contract on the balloon is restored almost to the range encountered in the

undistended control loop. This finding suggests that the passage of a long intestinal tube down the bowel in an obstructed, distended patient possibly will be hastened by subjecting the patient to increased atmospheric pressure.

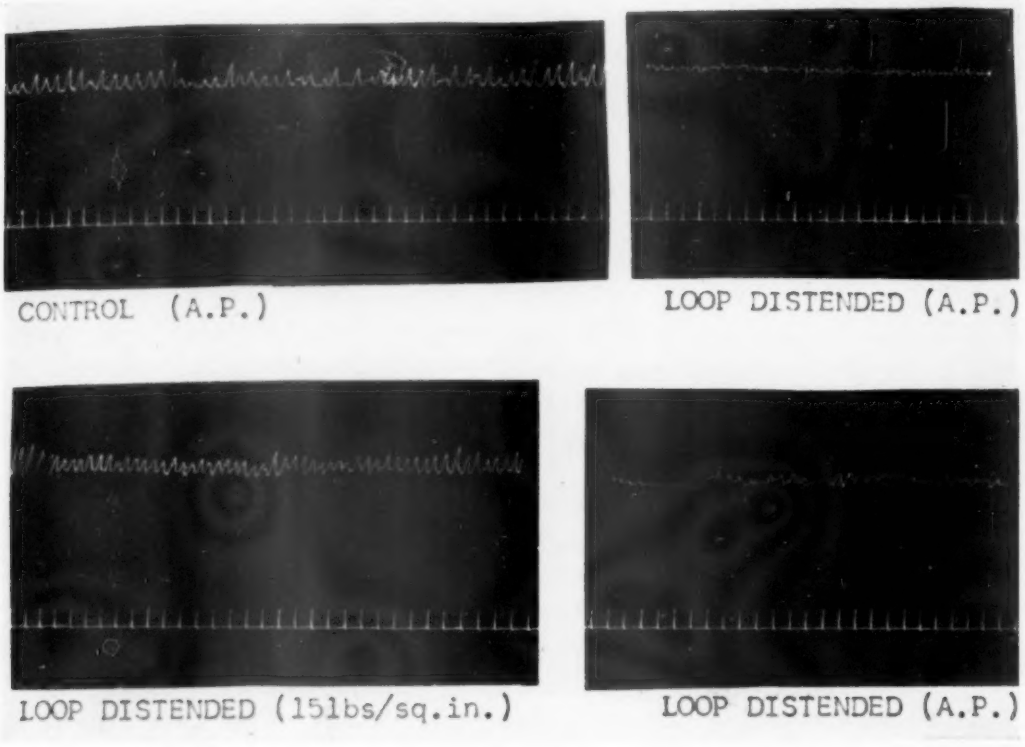


Fig. 7.—Dog 62. The effect of increased atmospheric pressure on the contractility of the bowel in a closed-loop obstruction.

Time equals 6 seconds.

A.P. equals 1 atmospheric pressure.

15 lbs./sq.in. equals 2 atmospheres pressure.

(From Cross, F. S.: Proc. Surg. Forum, Clin. Congress Am. Coll. Surgeons, 1952, Philadelphia, 1953, W. B. Saunders Company.)

DISCUSSION

Not only is there an increased diffusion of gas from the bowel under conditions of increased atmospheric pressure, but also the tone and viability of the bowel are well maintained. The magnitude of the increased rate of diffusion is directly proportional to the increase in the atmospheric pressure. For oxygen and for helium-oxygen mixtures, this increase averaged 7.4 per cent in a six-hour period when the pressure was increased from 1 atmosphere pressure to 2 atmospheres pressure. In those dogs breathing air, the increase in diffusion from closed-loop obstructions was 16.6 per cent in twenty-four hours when the pressure was raised from 1 atmosphere pressure to 2 atmospheres pressure, and 7.0 per cent for each additional rise of 1 atmosphere of pressure up to 4 atmospheres.

It is not possible to give a simple explanation for this increased diffusion of gas from the bowel with increasing pressures. Kety[35] has discussed the complexity of the physiologic parameters, such as pulmonary ventilation, car-

diac output, solubility and partition coefficients, diffusion processes, and diffusion coefficients, which are involved in such gaseous exchange. Whereas it is not possible to evaluate all these parameters in the scope of the present study, there are certain local changes, such as circulatory stasis and decreased blood-tissue diffusion rates, increased membrane thickness due to edema of the bowel wall, intraluminal fluid competing with gas for surface area of diffusion, and less favorable partial pressure diffusion gradients existing in the nonpressurized, distended loops, which combined to lessen the gaseous diffusion from those loops as compared to well-preserved, pressurized loops.

From the previously tabulated data, it can be seen that, although other gas-pressure-time schedules may have given better ultimate gaseous diffusion from the bowel, the best all-around schedule in terms of maximum diffusion in a minimum time was the inhalation of 95 per cent oxygen for six hours at 2 atmospheres pressure. Beyond this point, the law of diminishing returns sets in, for in the next six hours only 18.6 per cent more of the total injected gas leaves the bowel, giving a diffusion rate of 63.3 per cent when 95 per cent oxygen is inhaled for a 12-hour period. In addition, the incidence of oxygen intoxication increased from none in the six-hour period to 100 per cent in the twelve-hour period at 2 atmospheres pressure. There was no advantage in increasing the pressure in the six-hour period because oxygen intoxication again approached 100 per cent for pressure over 2 atmospheres, and the diffusion of gas from the bowel was not increased.

Helium-oxygen mixtures, unless used in combination with oxygen, did not give satisfactory diffusion rates. As mentioned previously, these poor results were due to the diffusion of helium into the bowel as the nitrogen diffused out sufficiently rapidly for it to constitute 15 per cent of the residual gas after six hours. Because of its low solubility coefficient in the blood, helium is then very slow to leave the bowel. Troell,[58] on the contrary, using 40 per cent helium-60 per cent oxygen mixtures, found that helium diffusion into the intestine is of such a magnitude that it is of no importance in the voluminal reduction.

Various gas combinations were tried in an attempt to prolong the exposure, at the same time obtain good rates of diffusion with minimal oxygen intoxication. The most satisfactory combination in these experiments was the use of oxygen-air-oxygen at six-hour intervals for a total of eighteen hours at 2 atmospheres pressure. The absorption was 63.3 per cent, and oxygen intoxication was not a real problem in this group. The various combinations of oxygen and helium-oxygen mixtures either did not give sufficiently better rates of diffusion to warrant the added expense of their use, or the incidence of oxygen intoxication was too great, as with the use of 60 per cent helium-40 per cent oxygen.

An important influence of increased atmospheric pressure on distended obstructed loops is the maintenance of the viability of these loops. At 1 atmosphere of pressure, 70 per cent of the closed loops showed evidence of loss of viability or function in a period of twenty-four hours. Sperling and Wangensteen[56] found a similar loss of viability in closed loops using sustained

pressures of 10 to 40 cm. of air or fluid for twenty-four hours. Van Beuren[59] has pointed out that as the gut distends, there is elongation and compression of the vessels in the wall, causing decreased blood flow, especially at the antimesenteric border of the bowel. Van Zwalenburg[61] and Dragstedt, Lang, and Millet[14] have adequately demonstrated experimentally this decrease in blood flow in the wall of the bowel with increasing intraluminal pressures. In addition, Lawson and Ambrose[37] and Gatch and associates[23] have described the opening of low-pressure vascular shunts in the intestine, distended to 30 cm. of water pressure, which short-circuit some of the tissue of the gut wall, depriving it of oxygen, and thus increasing the likelihood of necrosis. The ability of gaseous distention per se to exert sufficient pressure to produce gangrene of the bowel by means of compressive occlusion of the vessels in the wall has, therefore, been adequately demonstrated by the present experiments, and those of previous investigators.

Decreasing the degree of distention of the bowel by increasing the atmospheric pressure avoids these changes by decreasing the hydraulic stress factor on the wall of the gut. In the dogs pressurized at from 2 to 4 atmospheres, only 6 per cent of the obstructed loops showed signs of loss of viability and function, and these were of a minimal nature.

Distention is the best stimulus for exciting activity of the smooth muscle of the intestine[9]; however, prolonged distention by increased intraintestinal pressures causes fatigue of the smooth muscle, which in turn results in loss of tone and distention of the bowel.[17] It is important, therefore, in the obstructed gut to relieve the distention before it results in such secondary changes.

It has been shown in this study that the contractions of a recording balloon in a distended loop of gut were greater at 2 atmospheres pressure than at 1 atmosphere pressure. There are two possible explanations for this occurrence. Either effective peristaltic activity was restored to the overdistended smooth muscle of the bowel through the decreased distention of the gut at 2 atmospheres pressure, or the effect of the increased atmospheric pressure was merely to decrease the size of the bowel down to where its contractions were more satisfactorily recorded on the recording balloon, which stays uniform in size. It is hoped that no matter what the explanation, the practical implication will be the same; that is, by the use of compression, the passage of the long intestinal tube in cases of primarily gaseous distention will be accelerated. This thesis is being explored at the present time.

From the results of this experimental study, it is reasonable to feel that the use of increased atmospheric pressures will be of practical value in the treatment of certain clinical cases of bowel obstruction, primarily from the standpoint of the benefits gained through the maintenance of viability of the bowel wall, the increased gaseous diffusion from the lumen, and the subsequent accelerated passage of a long intestinal tube down the gut.

CONCLUSIONS

1. The rate of diffusion of gas from closed-loop obstructions was increased by means of increased atmospheric pressure per se.

2. The most satisfactory schedule for the absorption of gas from closed-loop obstructions in terms of maximal absorption in minimal time was the use of 95 per cent oxygen at 2 atmospheres pressure for six hours, resulting in the absorption of 44.8 per cent of the injected air.

3. Oxygen intoxication became a significant factor in those dogs inhaling 95 per cent oxygen when the pressure was increased above 2 atmospheres in a six-hour period, and when the time of exposure extended beyond six hours at 2 atmospheres pressure.

4. Helium-oxygen mixtures were not an effective substitute for 95 per cent oxygen because helium diffused into the bowel as the nitrogen diffused out, thereby partially maintaining the distention of the closed loops.

5. The viability of the bowel in closed-loop obstructions was well preserved for periods up to ninety-two hours by the use of increased atmospheric pressures.

6. The increased ability of the bowel in distended closed-loop obstructions to contract on a standard-sized bolus under conditions of increased atmospheric pressure was demonstrated.

7. The application of these experimental results to clinical cases of obstruction has been suggested.

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Appraisal of Progress in Surgical Therapy

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THE SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS

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ONE of the greatest accomplishments in thoracic surgery has been the surgical treatment of pulmonary tuberculosis. The development of surgical procedures for this purpose began approximately five decades ago. Although encouraging progress was made during the first half of this period, evolution of new concepts in the management of this condition was delayed until within the past decade. For this reason an appraisal of the current trends in the surgical management of pulmonary tuberculosis is timely.

That much progress in this field has been made in recent years is well illustrated by comparing the results obtained from surgical treatment one decade ago with those usually anticipated at the present time. For example, in 1934, arrest of the disease following a thoracoplasty could be expected in not more than 50 to 60 per cent of the patients, whereas today it may be anticipated in 80 to 90 per cent. Even more striking is the improvement following excisional procedures. Prior to 1940 the mortality of lobectomy was approximately 25 per cent, while that of pneumonectomy was 45 per cent. In addition, a considerable number of lesions remained active following surgery. In contrast, the risk in these surgical procedures has at the present time been reduced to less than 5 to 10 per cent, respectively, in properly selected cases. Furthermore, the disease process will be arrested in 80 to 90 per cent of patients surviving surgery.

The present-day concept of surgical management of pulmonary tuberculosis remains in an unsettled state. There is considerable variance of opinion as to the best type of surgical management of different pathologic forms of this disease. Likewise, there is as yet no universal agreement as to the indications and contraindications for various surgical procedures. Several outstanding developments have taken place during the past ten to fifteen years which have markedly improved the outlook of surgical therapy for this disease. These same factors have contributed materially to the present unstabilized thinking as to the use of various surgical procedures. This is due in part to the fact that many lesions will respond equally well to two or more methods of management.

Chief among the advancements has been the discovery of chemotherapeutic agents which are effective against the tubercle bacillus. These agents include

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streptomycin (Schatz and Waksman,[1] 1944), para-aminosalicylic acid (PAS), and isonicotinic acid hydrazide (isoniazid, 1952). These drugs administered alone or more often in combinations, when combined with bed rest and other supportive measures, have not only improved the status of the pathologic process prior to surgery and thus reduced the magniutde of the operation as well as preserved a greater percentage of pulmonary function, but have also greatly reduced the risk of operative procedures and have usually contributed materially in increasing the percentage of arrested cases following surgery. These drugs have been largely responsible for the marked reduction in mortality following resection of the lung, at the present time, as compared to that of one decade ago.

A second factor of considerable significance in the improvement of surgical management of pulmonary tuberculosis has been the development of techniques for pulmonary resection and their application to the management of this condition. Although these procedures had been previously evolved and applied in the treatment of bronchiectasis and carcinoma of the lung, their application in the field of pulmonary tuberculosis was unsafe until chemotherapeutic agents became available. At the present time, excisional therapy for tuberculous lesions enjoys wide usage. Indeed, in some areas this type of management has almost completely replaced the previously developed methods of collapse therapy. Changes in the pathologic status of the disease which at present confront the surgeon have undoubtedly played a major role in this shift from collapse to excisional type of therapy.

A third factor of importance has been improvements in tests of pulmonary function and the recognition of their clinical value. As judged by present-day standards, tests available for this purpose were of relatively little value prior to the last decade. Although our present methods leave much to be desired and will no doubt continue to be improved, much information can now be obtained which, when correlated with x-ray films, physical findings, and clinical course of the patient, aids materially in the choice of operative procedure most efficacious for each patient. Indeed, not infrequently surgical management of the disease process may depend largely upon clinical evaluation of pulmonary function studies.

A fourth advancement during the past decade has been improvement in methods of collapse therapy. For this purpose several techniques have been developed, all based on a common principle, that is, a selective type of complete collapse of the lung produced by a one-stage operation and with preservation of maximum pulmonary function. These procedures involve essentially a modified type of thoracoplasty, with the removal of few or no ribs and using a prosthesis for completely maintaining the collapse. The objectives of these newer techniques have been: (1) a higher percentage of arrested cases following operation; (2) a one-stage operative procedure; (3) avoidance of postoperative deformity; and (4) preservation of maximal lung function. All four of these objectives have been accomplished by these procedures without increasing the risk of operation or the frequency of complications.

The objectives of surgical therapy in the treatment of pulmonary tuberculosis may be defined as: (1) permanent arrestment of the disease; (2) preservation of function of the uninvolved lung tissues; (3) prevention of complications of surgical management; and (4) early re-establishment of useful activity of the individual. Securing these objectives depends upon a number of factors, that is: (1) the character and distribution of the pathologic lesions, (2) the status of the course of the disease at the time of surgery, and (3) the method of surgical management.

One of the most important considerations in surgical management of tuberculosis is the proper selection of patients for operation. In evaluating the tuberculous patient for surgery, a number of factors concerned with the status of the disease must be taken into consideration. These factors consist of (a) entire duration of the disease; (b) duration of the present problem presented by the patient; (c) status of the activity of the disease; (d) distribution of the lesion, whether unilateral or bilateral, or the amount of lung involved; (e) type and status of nonsurgical therapy; (f) presence and extent of extrapulmonary disease; (g) physical factors, such as obstructed cavity; and (h) consideration of host's resistance. These factors will have a direct bearing not only on the time of operative intervention, but also on the type of surgical procedure indicated for each patient. In the evaluation of a patient for surgery, not only should the history, physical findings, and laboratory examinations be carefully scrutinized, but, in addition, various tests to determine cardiopulmonary reserve should be made in order to have a complete evaluation of the problem.

SURGICAL PROCEDURES

The functions of surgical procedures in the management of tuberculosis may be divided into four groups, that is: (1) local rest and relaxation of the tissues, (2) collapse of the diseased process, (3) removal of the diseased process, and (4) drainage of cavities (see Table I).

TABLE I. OBJECT OF SURGICAL PROCEDURES IN THE TREATMENT OF PULMONARY TUBERCULOSIS

1. Rest and relaxation of tissues
(a) Phrenicotomy with or without pneumothorax or pneumoperitoneum
(b) Intrapleural pneumonolysis with pneumothorax
2. Collapse of the disease process
(a) Extrapleural pneumonolysis with prosthesis
(b) Thoracoplasty
(c) Extrafascial collapse with prosthesis
3. Excisional therapy of the disease process
(a) Pneumonectomy
(b) Lobectomy
(c) Segmental resection and local excision
4. Drainage of cavity

The general principles governing all surgical management of pulmonary tuberculosis are: (1) preoperative determination of pulmonary reserve; (2) the use of anesthesia which assures adequate circulation and oxygenation during operation; (3) employment of a surgical approach providing adequate exposure;

(4) maintenance of blood volume during surgery by replacement of blood loss; and (5) postoperative care which provides adequate oxygenation of the vital tissues and control of infection.

PRESENT STATUS OF OPERATIVE PROCEDURES USEFUL IN THE TREATMENT OF PULMONARY TUBERCULOSIS

I. *Phenic Nerve Crush and Resection.*—Paralysis of one side of the diaphragm may be made temporary or permanent according to the indications for the procedure. Crushing of the phrenic nerve in the cervical region and division of accessory branches will lead to paralysis of the diaphragm on the same side for four to six months' duration. This procedure is used much more frequently than division and avulsion of the phrenic nerve, which produces permanent paralysis. Local rest and relaxation of the pulmonary tissues are thus obtained on that side of the chest. No actual collapse of the tissues occurs. The indications for operations on the phrenic nerve have varied considerably since use of this procedure in pulmonary tuberculosis was first reported by Sauerbruch in 1913.[2] At the present time a temporary type of paralysis of the diaphragm is much more commonly employed. The indications for phrenicotomy may be roughly divided into three main groups, as follows: (1) to aid in pneumothorax or pneumoperitoneum treatment of tuberculosis; (2) in preparation for more major surgery at a later date; and (3) as a definitive procedure in patients where surgical interventions of greater magnitude are contraindicated. It is frequently impossible to evaluate accurately the beneficial effects of various forms of medical and surgical management in the treatment of pulmonary tuberculosis. This holds true also following paralysis of the diaphragm. Phrenicotomy was once thought to be of more value when the tuberculous lesion was located in the lower half of the lung. This, however, is not true in those instances where large cavities in the superior segment of the lower lobe have a check-valve communication with the bronchial tree. This operation has probably little value in those cases of chronic fibrocavernous tuberculosis located in the extreme apex of the lung. In general, phrenicotomy is thought to be more frequently indicated under the following circumstances: (1) for lesions with cavities not over 3 cm. in diameter and in the absence of marked production of scar tissue; (2) for earlier lesions with infiltration but without too great destruction of pulmonary tissue; and (3) in patients where pneumoperitoneum and pneumothorax are inadequate and where operations of greater magnitude are refused.

Although phrenicotomy is not complicated when properly performed, it should not be undertaken lightly. Of paramount importance is a thorough knowledge of the anatomy involved. The sympathetic chain and the vagus nerve have been mistaken for the phrenic nerve. The risk at operation is small, hemorrhage being the main serious complication, and this is quite uncommon. Air embolism has been reported, and injury to the thoracic duct on the left side can occur. Since pulmonary resection has become a safe procedure, phrenicotomy has lost much of its former usefulness.

II. *Intrapleural Pneumonolysis.*—The severing of adhesions between the diseased lung and the chest wall where pneumothorax has been inadequate was first performed by Hans Jacobaeus in 1913.[3] Prior to the advent of chemotherapy and resectional therapy, this type of pneumonolysis was a widely used procedure in the control of tuberculosis. A specially devised thoracoscope, first developed by Unverricht in 1925[4] and later modified by a number of workers, permitted the performance of this operation by means of cannulae introduced through the chest wall. The original procedures made use of a two-cannula technique. Both the two-cannula and one-cannula types of procedure are carried out at the present time.

Complications: 1. *Hemorrhage.* Although bleeding is usually in the form of slow venous oozing, sharp bleeding from an artery may occur. In most cases this can be controlled by cautery. Secondary hemorrhage following surgery can occur and must be guarded against by adequate cauterization at the time of operation. When bleeding is sharp or persistent, open thoracotomy should not be delayed.

2. *Empyema with or without bronchopleural fistulas.* The frequency with which this complication is seen depends upon the type of adhesions to be divided. Small stringlike adhesions seldom cause trouble following division. In the presence of larger adhesions or bands of pulmonary tissue, an active infectious process can project outward toward the wall further than would appear to be the case. The fact that the adhesion is present is an indication that infection at one time involved the inner surface of the chest wall. Pleural effusion occurs in some degree in approximately 50 per cent of these patients following surgery. Nontuberculous infection is rarely seen except in those cases where bronchial pleural fistulas develop. In such instances the infection may be a mixed one and will call for abandonment of the procedure and the employment of other measures. Like phrenic nerve operations, pneumonolysis has lost most of its usefulness since chemotherapy and excisional surgery have become available.

III. *Extrapleural Pneumonolysis With Prosthesis.*—This operative procedure produces actual collapse of the lung. The aim is to obtain a selective and complete collapse of only the diseased portion of the lung, with preservation of as much pulmonary function as possible. This operation was first performed by Tuffier[5] in 1911 and Baer[6] in 1913 and has been modified frequently since that time. Various materials have been used as a prosthesis including fat, muscle, rubber balloon, plastic substances, paraffin, and Fiberglas. Paraffin or plastic spheres are most often used at the present time. Since collapse therapy is now less often indicated than formerly, this procedure has lost much of its former value. The chief indication for this procedure is a disease process limited to the apex in patients with low pulmonary reserve and where cavitation does not reach the surface of the lung. Other factors of significance in recommending this procedure are bilateral distribution of the infection, apical lesions in young women, and instances where for psychologic reasons other

operations have been rejected. Contraindications include: (1) large peripheral cavities; (2) marked fibrosis at the apex of the lung; (3) lung densely adherent at the periphery; and (4) cavities located outside the apex.

The principal advantages of this procedure are: (1) production of a localized and selective collapse; (2) retention of maximal function of normal lung tissue; (3) minimal deformity of the chest wall; and (4) necessity of only a one-stage operation, thus insuring less discomfort, more economy, and greater cooperation of the patient.

Complications: Although a number of complications, such as infection of the extrapleural space by tuberculous and nontuberculous organisms, bronchopleural fistulas, and secondary hemorrhage, have been reported, these are primarily a result of poor selection of patients for operation. When the operative procedure is not extended beyond its limitations, postoperative complications should be comparatively infrequent. In my experience, the incidence of spread of the infection on the same or contralateral side following this procedure has not been greater than after the conventional form of thoracoplasty. When the operation is limited to those patients having small apical cavities not located adjacent to the parietal pleura, the previously mentioned complications are seldom observed. Secondary hemorrhage in this space may be prevented by careful hemostasis during surgery. Because of the selective type of collapse produced in a single-stage operation, this procedure gained considerable favor over the conventional type of thoracoplasty for patients with less-advanced lesions. At the present time I favor the extrafascial-extraperiosteal type of collapse, to be described under the heading of thoracoplasty.

IV. *Extrapleural Paravertebral Thoracoplasty.*—This operative procedure was first designed to collapse a diseased lung by Gerenvill in 1885.[7] It was modified by a number of workers in order to obtain increased effectiveness and decreased surgical risk. The conventional present-day thoracoplasty is patterned somewhat after the Brauer[8] type of operation, with the exception that it is performed in several stages in order to reduce the risk of the procedure.

With more prompt and effective care now available for patients with pulmonary tuberculosis, the indications for thoracoplasty have become less frequent. They include: (1) fibrocavernous lesions at the apex of the lung, especially in the presence of bilateral active disease; (2) as a preliminary procedure to resection in some bilaterally active lesions; (3) where pulmonary function is considered inadequate for safe excisional therapy; and (4) where the extent and character of the disease or the presence of extrapulmonary lesions makes resection hazardous. Although it is difficult to compare accurately the results of collapse and excisional therapy in regard to advantages, disadvantages, and risk, in general it may be said that for far-advanced fibrocavitary lesions, thoracoplasty will carry less risk than resection, may produce a greater reduction in pulmonary function, and in some types of lesions will not yield as high a percentage of arrested cases. Two very real disadvantages of the conventional type of thoracoplasty are: (1) the necessity of performing a several-stage operation and (2) some degree of accompanying scoliosis with mild dis-

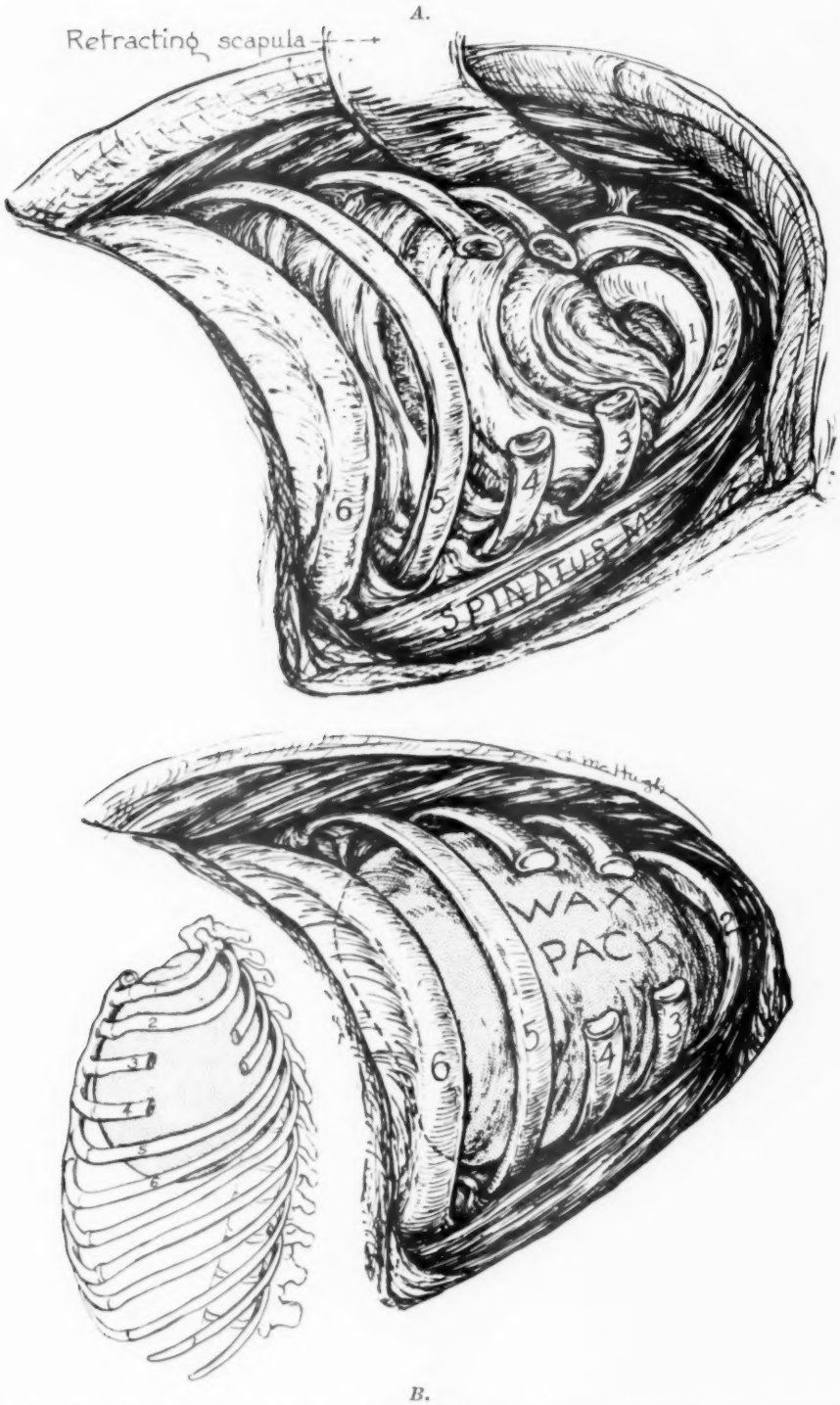


Fig. 1.—*A*, Drawing to illustrate the appearance of the collapsed area following freeing of the periosteum and intercostal structures from the first five ribs in the treatment of pulmonary tuberculosis. Note that the structures are depressed from beneath these ribs and that long segments of the third and fourth ribs remain.

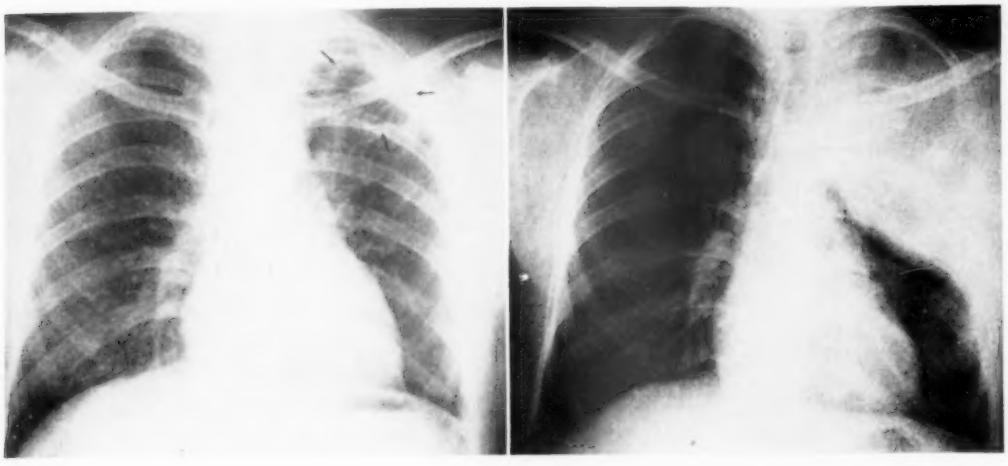
B, Drawing to show appearance of chest with a wax prosthesis placed beneath the ribs from which the soft parts have been mobilized. Note selective nature of collapse. By resecting only short segments of two ribs, no scoliosis results and the wax is better maintained in position.

figurement of the body and with reduction in pulmonary function. With the conventional type of thoracoplasty, one can anticipate arrestment of the disease in approximately 75 to 80 per cent of patients according to the nature and extent of the disease.[9]

IV. (a) *Thoracoplasty With Extrafascial and Extraperiosteal Paraffin Prosthesis.*—Because of the deficiencies of the conventional thoracoplasty, attempts have been made to produce a more selective type of collapse by a one-stage procedure. The technique which I devised some eight years ago entails the use of an extrafascial prosthesis of paraffin placed in the collapsed area after mobilization of the periosteum and intercostal structures from the ribs. This procedure has been modified from time to time. The present technique may be described as follows: Through an incision posteromedial and inferior to the scapula, the bony thorax is exposed. In a one-stage operation, long segments of the ribs from the first to as low as the eighth (as indicated) are denuded of their periosteum. After division of the serratus posterior superior muscles adjacent to the spine, and freeing of the posterior ends of the intercostal muscles, the periosteum and intercostal muscles are depressed beneath the ribs. Short segments (two or three inches) of the third and fourth ribs are removed beginning approximately one inch lateral to the angle of the rib posteriorly. The periosteum of the first rib is mobilized only from its inferior surface. Following this, an apicolysis is performed, mobilizing the lung from beneath the cupola of the pleural cavity. This allows a selective type of collapse extending from the apex of the pleural cavity downward as far as desired (see Fig. 1, *A*). The collapse of the lung is maintained by a prosthesis of paraffin. Material with a melting point of 50° to 52° C. is used after previous sterilization. During surgery it is melted and then allowed to cool so that the plombe can be molded as it solidifies and while it is reaching the proper temperature for application (see Fig. 1, *B*).

After the molded paraffin is placed in the collapsed area, the chest wound is closed in layers in the usual fashion without drainage. In an experience covering the use of this procedure in over 450 patients during the past seven years,[10, 11] several noteworthy advantages have been observed as compared to the conventional type of thoracoplasty, that is: (1) increased percentage of arrested cases (85 to 90 per cent), (2) a single-stage operation, and (3) obviation of scoliosis and resultant deformity, thus minimizing reduction in pulmonary function. Complications observed following the use of this procedure have been minimal. There have been no instances of deep wound infections or bronchopleural fistulas. Spread of the disease to the same or to the contralateral side has not been observed more often than following the conventional type of thoracoplasty. Before the previously described technique was put into use, migration of the wax outward was observed in a small percentage of patients, thus necessitating removal of at least a portion of the wax. In those cases, however, arrestment of the disease had usually already been accomplished, and removal of the wax was only a minor procedure.

V. *Resection Therapy of Pulmonary Tuberculosis.*—Although excisional therapy for pulmonary tuberculosis was first suggested by Forlanini approximately seventy years ago and attempted by Ruggi[12] in 1884 and by Tuffier[13] in 1897, this type of management became practical only during the past decade. The early results were far from encouraging. However, with the advent of chemotherapy for pulmonary tuberculosis and the application of improved surgical techniques, this form of management has become the one of choice in an increasing number of patients.



A. *B.*

Fig. 2.—*A*, X-ray film of chest of a 27-year-old East Indian student who had had pulmonary tuberculosis for several years. The patient improved temporarily and then his condition became stationary. The tubercle bacilli became insensible to all chemotherapeutic agents. Note large cavity in left apex measuring 3 to 4 cm. in diameter. This patient had had bilateral involvement, although at the time of surgery the disease in the right lung was stationary.

B, X-ray appearance of the chest approximately seven weeks following a single-stage modified thoracoplasty with subscapular extrafascial paraffin prosthesis. Note selective nature of collapse with preservation of aerated lung tissue below. The lesion in the right lung has remained stationary. Following operation the patient's sputum has been converted and he has been completely relieved of symptoms.

One of the major factors in the success enjoyed by this form of therapy has been alteration in character and decrease in extent of the disease by the use of chemotherapy prior to surgery. Because of the increasing safety of operation and high percentage of successful results, the value of pulmonary resection is ever increasing. At present its indications are as follows: (1) thoracoplasty failure; (2) the presence of lower lobe lesions, particularly cavities in the superior segment, or tuberculosis with secondary bronchiectasis; (3) destroyed lung; (4) closed (active) tuberculous lesions; (5) indeterminate pulmonary lesions where malignancy cannot be excluded; and (6) very large cavities.

In dealing with smaller isolated lesions, excisional therapy enjoys a number of advantages over the conventional thoracoplasty, that is: (a) it is selective in type and is more conservative of pulmonary function; (b) only a one-stage operation is required; and (c) little or no postoperative deformity occurs. (The latter two do not apply to extrafascial plombage combined with thoracoplasty.)

The principal contraindication to excisional therapy is the presence of advanced bilateral fibrocavernous lesions of considerable magnitude in patients having poor host resistance and with tubercle bacilli no longer sensitive to chemotherapy.

Although the mortality and morbidity following excisional therapy have been markedly reduced following the use of chemotherapy, complications still occur in patients with lesions of considerable magnitude. Those complications most commonly observed are (a) bronchial obstruction with atelectasis of remaining lung tissue, (b) contralateral or ipsilateral spread of the disease, (c) bronchopleural fistula with tuberculous empyema and spread of infection, and (d) spread of the tuberculous infection to extrapulmonary tissues such as the mediastinum and pericardium. Of these complications the one to be most feared is bronchopleural fistula. The mortality following excisional therapy for pulmonary tuberculosis is largely based on this latter complication, which occurs more frequently following pneumonectomy or lobectomy than after segmental resection if this latter procedure is not pushed beyond its limitations.

GENERAL CONSIDERATIONS

I. Position of the Patient.—Of the three principal positions for performing intrathoracic operations, that is, lateral, supine, and prone, the former is most often used except with patients raising considerable quantities of secretion. Because of the previous tendency of the infection to spread to the lower lung, the prone position gained favor, and at the present time some surgeons consider it the position of choice.

II. Anesthesia.—Although many anesthetic agents and methods are employed in excisional therapy, a general tendency to the use of simpler methods and mixtures has recently been observed. Ether-oxygen has gained greater favor because of its wide range of safety and the absence of depression of the respiratory center. Normal ventilation should be assured and oxygen administered in adequate amounts.

OPERATIVE PROCEDURES

I. Pneumonectomy.—Total ablation of the lung is used much less frequently than lobectomy and other smaller resections. Since preservation of a portion of the lung is possible in most patients, it is largely employed in patients with a destroyed lung or where thoracoplasty has failed to arrest the disease.

There is still no universal agreement as to whether pneumonectomy should be preceded or followed by collapse of the chest wall. In my experience, complications have been fewer and the mortality has decreased when collapse of the chest wall has preceded resection. Furthermore, with the pleural space obliterated, the remaining lung is less likely to become overinflated, thus tending to impair pulmonary function. This is especially true in patients following complete ablation of the right lung. Some surgeons prefer to collapse a portion of the chest wall at the time of surgery or at some subsequent period rather than prior to resection. This is especially advisable in patients with ten-

sion cavities or where expectoration is profuse. Collapse of the diseased process prior to resection under these circumstances is likely to give rise to a spread of the disease in the ipsolateral or contralateral side.

II. Lobectomy.—Although pulmonary tuberculosis may occur in any part of either lung, it is much more commonly located in the upper lobes, and thus upper lobectomy is more frequently performed than lower lobectomy. The procedure is carried out in a similar manner on either side. I prefer an approach through the fifth intercostal space. For a lower lobectomy, the approach is usually made through the seventh intercostal space with removal of short segments of the seventh and eighth ribs posteriorly. Otherwise, the technique for the procedure is similar to that employed in upper lobectomy.

The question of whether a tailoring thoracoplasty should be used following upper lobectomy continues to be debatable. When the remainder of the lung on the same as well as the opposite side shows little or no evidence of involvement, there appears to be little indication for the use of a tailoring thoracoplasty. However, for those patients who have had widespread involvement by a tuberculous process, reduction of the pleural space following lobectomy is likely to be indicated. Following lower lobectomy, paralysis of the diaphragm by division (or crushing) of the phrenic nerve will accomplish this purpose. In upper lobectomy, a tailoring thoracoplasty either prior to resection, at the time of lobectomy, or a short time thereafter should be employed. Following resection of the lung in either upper or lower lobectomy, the wound is closed in layers with drainage of the pleural space by means of continous suction applied to an intercostal tube drain.

III. Segmental Resection of the Lung.—With the increasing possibility of controlling tuberculous lesions of the lung by means of chemotherapy, a greater number of patients are referred for surgery with better controlled and much more localized lesions. Many of these patients present small closed lesions or small localized fibrocavernous lesions limited to one or two segments of a lung lobe. Segmental resection of pulmonary tissue has been used in the treatment of nontuberculous bronchiectasis over the past two decades.[14, 15] However, the use of this procedure in the treatment of tuberculous lesions was begun less than one decade ago.[16, 17] Because of the decreasing severity of pulmonary tuberculosis, largely resulting from the use of chemotherapy, the indication for segmental resection has increased materially during the past few years. Although there is as yet no universal agreement as to the indications for this procedure, accumulated experience has revealed the following pathologic types of lesions favorable for its use: (1) fibrocavernous lesions limited to one or two segments and with no active infiltrative process outside the segment to be resected; (2) closed tuberculous cavities which have filled in with inspissated material and which remain a potential hazard to the patient; and (3) chronic localized tuberculous lesions, whose nature cannot be determined by other than microscopic section.

Segmental resection in the treatment of pulmonary tuberculosis is more frequently carried out in the upper lobes. The next most common site is the

superior segment of the lower lobes. The extent of resection is determined at the time of exploration when the findings can be correlated with the clinical and x-ray findings. Planograms not infrequently provide invaluable information upon which the resection is planned.

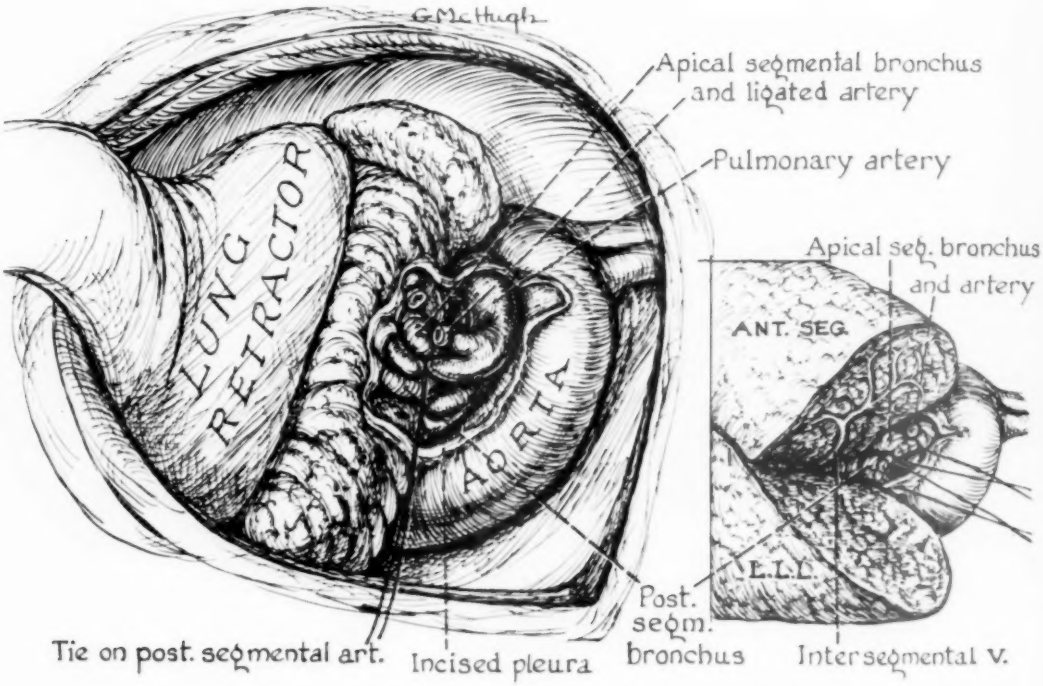


Fig. 3.—Drawing to illustrate operative technique for the resection of the left apical and posterior segments of the left upper lobe. The upper lobe is retracted downward and the bronchi and arteries to these two segments are mobilized. Insert shows the appearance following the removal of these two segments. Note (1) artery ligated, (2) segmental bronchi closed by interrupted suture, and (3) intersegmental vein which should be spared when the segments are removed. Only the anterior segment of the upper lobe remains. The two segmental bronchi will be covered by adjacent tissue.

Technique of Operation.—For upper lobe segmental resection, an approach is made through a posterolateral incision on either side, the thoracic cage being opened through the fourth or fifth intercostal space. Short segments of the rib above and below are removed posteriorly to facilitate exposure. For resection of the superior segment of the lower lobe, or for the middle lobes, the approach is made through a slightly lower incision (sixth or seventh intercostal space, as indicated). A knowledge of the normal anatomy of the parts involved as well as variations from the normal is essential in order to perform these operations safely. In some segments to be removed, more than one artery may be present. An example of this is the superior segment of the lower lobe. Dissection should begin at the hilum of the part to be extirpated and the arteries dissected free from the surrounding structures. Since the disease process, due to fibrosis and so forth, may have considerably altered the normal anatomy, accurate identification of the part of the lung supplied by the vessels must be made before they are ligated. A search should be carried out for unusual branches and their distribution should be noted before ligation is made. After

mobilization, double ligation, and division of the arterial supply, the bronchus to that segment is mobilized from the surrounding structures. Before division of the bronchus, it should be clamped proximally with a noncrushing clamp and the remainder of the lung should be inflated in order to determine whether

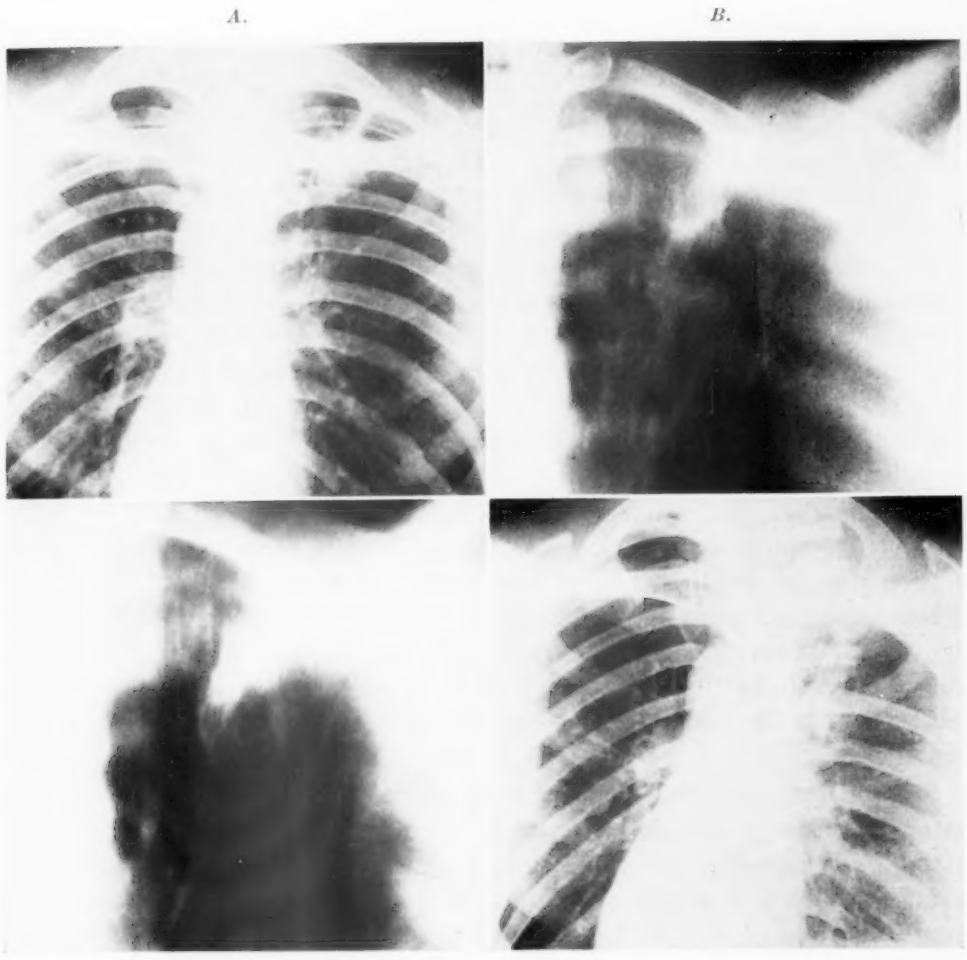


Fig. 4.—*A*, X-ray film of the chest of a white man 31 years of age, whose chief complaint was hemoptysis. Note absence of cavitary lesions in customary posteroanterior type of film.

B, Planogram of chest showing definite cavitary lesion in right apex.

C, Planogram of chest made five months later shows a persistence of cavitary lesion with scarring in right apex.

D, X-ray appearance of the chest eighteen days following resection of the posterior and apical segments of the right upper lobe for a fibrocavernous type of lesion. A small tailoring thoracoplasty was added.

the involved portion of the lung is supplied by the obstructed bronchus. The vein draining the segment to be resected is then identified, mobilized, and treated in a manner similar to that used for the arteries. The segment is then removed by a combination of blunt and sharp dissection, small vessels being clamped as the lung is separated from adjacent normal tissue. Since inter-

segmental veins are present between segments of the lung, these veins should be preserved, and only branches entering the part to be removed should be clamped and tied. After hemostasis has been obtained, the bronchial stump is closed with a single row of sutures. For this purpose I favor the use of a 000 or 0000 silk suture. The stump is then buried in tissue adjacent to that region. No attempt is made to suture the cut edges of the lung where the segment was removed since this tends to interfere with the blood and air supply of the adjacent lung and still further reduces the function of the remaining lung tissue. If, in dissecting the diseased segment away from the remaining lung tissue, the visceral pleural covering can be spared, this can be loosely applied over the cut surface of the remaining lung (see Figs. 3 and 4).

Long-term results following segmental resection of all types of lesions are not yet available. Most reports contain a large percentage of small closed cavities and isolated lesions. It is difficult to foretell accurately what may be accomplished by segmental resection for active open tuberculous lesions. It is fair to predict, however, that if the operation is not pushed beyond its limitations and the patient can be fortified by the use of chemotherapy before and following operation, results of this procedure should be favorable in a high percentage of cases (80 to 90 per cent).

Complications following segmental resection are similar to those following lobectomy and pneumonectomy. Most patients have tiny air leaks from the open parenchymal surface of the lung. However, with constant suction applied to the pleural space for maintenance of expansion of the remaining lung, these leaks close spontaneously within a few days. Spread of the tuberculous infection, bronchopleural fistula, and serious tuberculous empyema should occur with much less frequency than following pneumonectomy or lobectomy.

Since relatively little reduction in pulmonary tissue occurs after segmental resection, a tailoring thoracoplasty following this operation is seldom indicated. Where a considerable amount of lung tissue has been destroyed by the infection, a temporary reduction in the pleural space by crushing the phrenic nerve may aid in the period immediately following operation.

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Book Review

Surgical Technique and Principles of Operative Surgery. By A. V. Partipilo. Ed. 5. Pp. 704. Philadelphia, 1953, Lea & Febiger.

The fifth edition of A. V. Partipilo's *Surgical Technique and Principles of Operative Surgery* is designed to serve as a practical reference text for the surgeon.

Questionnaires are found at the end of most of the chapters and test the reader's assimilation of the material. The text is clearly and profusely illustrated, and the operative techniques described are those which have proved to be the most satisfactory procedures in the author's practices.

Chapters on kidney, chest, and plastic surgery are included, although the bulk of the book is devoted to general abdominal surgery.

This book should be of greatest value to the undergraduate medical student and to the medical practitioner.